Wilms tumor (WT) is the most common malignant neoplasm of the urinary tract in children, accounting for ~ 8% of all childhood solid tumors. These tumors are remarkable in attempting to recapitulate the different stages of nephron development, albeit abnormally. A tumor suppressor gene, WT1, implicated in predisposition to WT has been identified by positional cloning at chromosome 11p13. This gene has been extensively characterized and is implicated by mutational analysis in 10-15% of sporadic WTs and as playing a role in initiation of this disease.

Only a small proportion (5-10%) of individuals with WTs show evidence for a genetic predisposition to this disease. Among these, the majority of individuals are affected with one of three congenital malformation syndromes, characterized by a predisposition to WTs. These include: the WAGR syndrome, Denys-Drash syndrome and Beckwith-Wiedemann syndrome. Familial pedigrees showing susceptibility to WTs are very rare. Unlike individuals with WAGR or DDS, who carry germline WT1 mutations, male members of WT families do not show urogenital malformations and the frequency of parent-child pairs and sibling pairs within the kindreds are relatively infrequent.

To determine if the WT1 gene can also play an integral role in the development of some familial WTs, we analyzed the molecular status of this gene in a family showing paternal transmission of WTs to three of five offspring. Upon PCR-SSCP analysis of genomic DNA from several members of this family, we noted that the products of exon 8 (zinc finger II) demonstrated a mobility shift pattern suggestive of a germline mutation. Whereas the unaffected mother and child demonstrated 3 conformers of exon 8 by SSCP analysis, the PCR products of exon 8 from the proband and father were more complex, revealing an additional set of conforms for this exon. Analysis of DNA from the second WT of the proband revealed los of one set of conformers and retention of one set of conformers present in the proband and the father. This patten is classical for tumor suppressor gene analysis and suggests the unmasking of a recessive mutation by loss of the wild-type allele.

To characterize the nucleotide alteration responsible for the altered mobility pattern of exon 8 by SSCP, the PCR product from the WT specimen was cloned into PKSII+ and sequenced. We identified a C to T transition at nucleotide position 1084 (relative to the A of the ATG codon) of the WT1 tumor suppressor gene leading to a nonsense mutation at amino acid position 362 of the protein, within zinc finger II. This mutation is predicted to result in the production of a truncated WT1 polypeptide unable to bind DNA. We interpret these results to indicate that the WT1 gene can be involved in some cases of familial transmission of this disease.

P-38

CD34+/FLT-3+ CORD BLOOD PROGENITOR CELLS ARE ENRICHED IN MEGACARYOCYTE PRECURSORS:

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The flt-3 tyrosine kinase receptor is expressed on primitive hematopoietic cells and the ligand for this receptor has been cloned. In this work we were interested in the differentiating capacity of CD34+/flt-3+ progenitor cells derived from human cord blood. MATERIAL AND METHODS: CD34+ cells were isolated from 15 samples of cord blood using Magnet-Activated Cell Sorting (MACS) to a purity of 99%. After isolation, the CD34+ cells were further stained with an anti-flt-3 antibody. Cells were later separated in CD34+/flt-3- and CD34+/flt-3+ subpopulations using a Fluorescence-Activated Cell Sorter (FACSstar). The sorted cells were then further incubated in methylcellulose in the absence or presence of various cytokines and their combinations (Thrombopoetin (TPO), stem cell factor (SCF), Interleukin-3 (IL-3) and flt-3-ligand). The resulting clusters and colonies were counted and differentiated weekly for three weeks. RESULTS: In the presence of TPO, SCF, IL-3 and flt-3-ligand, the number of colonies and clusters was higher in the CD34+/flt-3- population compared to the CD34+/flt-3+ subpopulation. However by using this cytokine combination, the number of megakaryocyte precursors (CFU-Meg) was higher in the CD34+/flt-3+ population. Additionally the size of the CFU-Meg originating from the CD34+/flt-3+ progenitor subpopulation was larger compared to the CD34+/flt-3-. CONCLUSIONS: Sorted CD34+/flt-3+ hematopoietic progenitor cells are enriched in cells capable to differentiate to CFU-Meg in the presence of combinations of cytokines. These findings might be helpful for defining strategies for the ex-vivo expansion of megacaryocyte precursors.

P-39

ENHANCEMENT OF MEROCYANINE 540 PHOTOTHERAPY OF NEOPLASTIC CELLS BY HUMAN ALBUMIN. IMPLICATIONS FOR BONE MARROW PURGING.

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We studied the effect of Mc 540 mediated photoirradiation on both neoplastic and normal hemopoietic progenitor cells. Bone marrow cells from 26 children with acute leukemias ALL in remission and normal children, as well as cells of Reh-6 and HL-60 cell lines were incubated with MC 540 in the presence of Human Albumin (H. A.) and exposed to different Argon Laser 514nm doses. Cell survival was estimated by trypan blue supravital stain following a 24 hour incubation and leukemic cell lines have been studied in continuous cell cultures of 4 weeks' duration. Our results showed that although H. A protects normal B. M precursors from Mc 540 mediated phototoxicity, it has minimal effect on the survival of neoplastic cells at doses ≤ 0,25%. A 99.9999% inhibition of Reh-6 and HL-60 was noted at irradiation doses where the corresponding mean survival of normal bone marrow cells was 80.6±4% and 74.3±2.8% respectively. Fresh bone marrow samples from children with acute leukemias were also very sensitive to Mc 540 photoirradiation, although variability was observed in their sensitivity to Mc 540. H. A protected the erythroid progenitors of children with ALL in remission from the catastrophic effect of Mc 540 phototreatment. Finally, the survival of normal B. M progenitors was 36% for CFU-E, 48% for BFU-E, 53% for CFU-GM and 30% for CFU-GEMM. In conclusion, it seems that Mc 540 mediated photoirradiation exerts selective cytotoxicity in neoplastic cells and can be used in ex vivo purging of malignant cells in the bone marrow.

P-40

LOSS OF HETEROYIGOSITY (LOH) ON 9P21 AND 17P13 IN NEUROBLASTOMA

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Neuroblastoma is a paediatric malignancy with extremely variable prognosis. A high number of children suffering from these tumours die, while at the other extreme, a relatively elevated proportion may exhibit spontaneous remission. Therefore, it is important to identify genetic features other than N-myc amplification, which will enable further discrimination among neuroblastomas, as far as clinical behaviour is concerned.

We have screened a group of 24 neuroblastomas for LOH at regions 1p36, 17p13.1 and 9p21 using a series of microsatellite markers. LOH was detected in 4 tumours at 1p36 (17%), in 3 tumours at 17p13.1 (13%) and in 4 tumours at 9p21 (17%). In two of the tumours with LOH at 17p13 one of the alleles of the p53 gene was lost. N-myc amplification was detected in all tumours with 1p36 loss.

Analysis of the results indicate that LOH at the various loci congregated in 6 of the 24 tumours, 5 of which were stage IV. Three of the patients with such pattern of LOH in their tumours died of the disease.

These results seem to indicate that losses at 9p21 and at 17p13 are common events among advanced stage tumours (present in respectively 33% and 50% of stage IV tumours in this series) and may correlate with particularly poor prognosis. They also suggest an additional prognostic value for the simultaneous use of these genetic markers.

P-41

MARKERS OF INDUCED MDS AND LEUKEMIAS IN PATIENTS FROM THE REGION OF TCHERNOBYL ACCIDENT (KIEV REGION, UKRAINE)

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From April, 94 to April, 96 successful cytogenetic examinations of BM in 28 patients (age 11 m - 18 y) with MDS and AL from Kiev Region (including Tchernobyl district) were made. 10 pts. had AML, 13 pts. ALL and 5 MDS. Karyotypic abnormalities were recognized in 23 cases (82 %). 15 pts. with AL (65 %) and 4 pts. with MDS (from 5) had karyotypic aberrations which could be considered markers of induced disease, mainly caused by irradiation. For the total group the incidence of these markers were 68 %. The following changes were seen: ~4n in 7 cases (37 %); +8 (2 cases); ~3n; hypoploidy; del (7) (q35)/~4n; 5q-/~4n; inv (3)/~4n; -5. Two of 7 children with AML and 3 of 8 children with ALL and these markers were resistant to therapy or suffered early relapses; 2 of 4 pts. with MDS and these markers revealed fast transformation.

Conclusion: In literature the frequency of theses markers is about 10 % in pts. with leukemias and MDS. We could suppose that the unusual high incidence (68 %) of cytogenetic markers of induced diseases among patients from Kiev Region could be concerned result of radiation exposure due to the Tchernobyl catastrophe.

P-42

IMMUNOGLOBULIN VH3-POSITIVE AIDS-RELATED BURKITT'S LYMPHOMA: A POSSIBLE ROLE FOR THE HIV gp120 SUPERANTIGEN.

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Burkitt's Lymphoma (BL) is the second most common malignancy affecting AIDS patients and like endemic BL it is usually preceded by dysregulation of the immune system. Similarly to endemic malaria in the African BL model, HIV infection indirectly causes B cell proliferation but eventually leads to the depletion of the B cells expressing immunoglobulin VH3 gene products. It was recently shown that a subpopulation of normal B cells from non-HIV-infected individuals can bind to HIV gp120 by means of membrane Ig; most of these B cells expressed VH3 family Ig. gp120 selectively induced Ig secretion by VH3 B cells indicating that it functionally activated these cells. These results indicate that naturally occurring VH3 is a second ligand for gp120 making it a candidate superantigen for VH3 B cells.
Based on the very high incidence of BL among HIV-positive individuals we originally analysed tumor DNA samples from three affected pediatric AIDS patients for the usage of the VH3 subgroup. All three samples in this restricted group of patients were positive for this particular VH subgroup, in contrast to non-AIDS BL cases, where only one out of five cases had VH3 rearrangement. Subsequently we analysed a set of DNAs from the NCI and two out of two AIDS BL samples were VH3 positive while only three out of thirteen non-AIDS samples were VH3 positive. These results indicate a possible role for gp120 in lymphomagenesis.

P-43

INSTABILITY OF DINUCLEOTIDE REPEATS IN HODGKIN'S DISEASE

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Tumorigenesis has been shown to proceed through a series of genetic alterations involving protooncogenes and tumor suppressor genes. However, investigation of genomic instability of microsatellites has disclosed a new mechanism for human carcinogenesis, which is involved not only in hereditary nonpolyposis colon cancer (HNPCC) but also in a number of other malignancies.
To determine whether microsatellite instablility is involved in Hodgkin's disease (HD), we screened 16 such tumors using 7 microsatellite marker loci on 6 chromosome arms 4, 5, 9p, 9q, 11, 14 and 17.
Using the polymerase chain reaction method, DNA samples from the tumors and from normal peripheral blood leukocytes from each patient were compared for the allelic pattern produced at each locus. Six cases of genomic instability were identified suggesting that this mechanism is relevant to the pathogenesis of HD.

P-44

CYTOMEGALOVIRUS INFECTION IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA.

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In 114 children with acute lymphoblastic leukemia (ALL) were examinated immune deficiencies and was determinated the efficiency of therapy of CMV infection. Before the start of chemotherapy, examination of T-lymphocyte subpopulations indicated their redistribution: decrease of CD16+; CD3+ and CD4+ cells and increase of CD8+ cells (CD4+/CD8+=0,87). During therapy counts of T-lymphocytes were significantly increased ($p<0,01$) and absolute counts were decreased ($p<0,001$). Level of IgM was decreased from alexan phase of I protocol, and level of CIC was increased ($p<0,001$) till finishing stage of II protocol. Redistribution of CD4+ and CD8+ cells below 1,0 was noted uptill the finishing point of 2 protocol therapy. CMV infection was revealed in 28,1% of patients (32 out of 114) on clinical grounds and EIA-examination data. Treatment of pts with CMV infection in remission stage of ALL included acyclovir intravenously and immuno-modulator thymogen (17pts). Improvement of

hematological indices in this group maintened longer than in control group (15 pts without this therapy). Data obtained from our studies indicate that the treatment with acyclovir and thymogen are effective and substantiates in children with compromised T-cell function in dynamics of ALL-BFM-90 programme of complex therapy associated with CMV infection.

P-45

ALLOGENEIC BONE MARROW TRANSPLANTATION FOR CHILDHOOD LEUKEMIA FOLLOWING A PREPARATIVE REGIMEN CONSISTING OF BUSULFAN AND MELPHALAN.

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Since a regimen that includes total body irradiation (TBI) may induce late toxic effects in children, we have designed a treatment for allogeneic bone marrow transplantation (BMT) that consists of busulfan and melphalan without TBI. Patients and methods: From September 1988 to January 1996, 30 patients (age:9 months to 14 years) underwent BMT at our institute. Diagnosis included acute myelogenous leukemia (n=20), acute lymphoblastic leukemia (n=6), acute unclassified leukemia (n=2), and chronic myelogenous leukemia (n=2). A total of 25 grafts were performed during the first complete remission (CR), 3 during the second CR, and 2 during the chronic phase. The conditioning regimen cosisted of 4×4mg/kg busulfan and 3×60～70mg/m² melphalan. Graft versus host disease (GVHD) prophylaxis consisted of methotrexate (n=25) or methotrexate plus ciclosporin (n=6). Results: Engraft was achieved in all patients. There were no life-threatning complications. Feverand liver dysfunction were commonly observed, but none of the patients had veno-occlusive disease. Five patients (22%) developed acute GVHD; Four had grade Ⅰ and one had grade Ⅱ. Chronic GVHD was documented in 5 patients (25%). Three patients relapsed. Two received a second BMT, after which one died of interstitial pneumonia and one remained in remission with chronic GVHD. Two patients died. As of January 31, 1997, 27 patients have not relapsed. The disease-free survival (DFS) rate was 90%. The DFS was 88%, 100%, and 100% in patients treated during the first CR, second CR, and the first chronic phase, respectively. Conclusion: A regimen consisting of high-dose melphalan and busulfan without TBI is useful for the treatment of BMT in children with leukemia.

P-46

Toxicity of high- dose Melphalan, Etoposide and Carboplatin ± 131-Meta-Iodbenzylguanidin (mIBG) followed by stem cell rescue(SCR) in neuroblastoma patients

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Introduction: In neuroblastoma patients high dose treatment followed by SCR and treatment with mIBG is promising. We tested a high-dose therapy consisting of melphalan, etoposide and carboplatin ± mIBG and evaluated its toxicity.
Regimen: 559 ± 115 Mbq/kg mIBG was followed by melphalan : 4x 45 mg/m²/d (day -8 until day -5), etoposide : 1x 40 mg/kg/4h day -4, 2 x carboplatin 500 mg/m²/1h day -3; -2. The re-transfusion of the stemcells was followed by 10 µg/m² G-CSF (Neopogen ®) from day +1. In patients with mIBG therapy, kalium jodatum was applicated for three weeks. Ondansetron was used as an anticmetic.
Patients: 20 patients with neuroblastoma stage 4, previously treated according to the NB 90 protocol of the German Society of Pediatric Oncology, aged 1.8 to 10 years (mean 5 years). 13/20 patients had preceding mIBG therapy.
Evaluation: Toxicity was estimated using WHO score. Nausea was estimated using NCI criteria for its independency from the antiemtic schedule used. The duration and onset of the side effects were determined. The duration of mucositis was defined more exactly by estimating duration and maximum requirement of morphine.
Results: Following day 0, patients were discharged on day + 27 ± 10 days. The toxicity consisisted of haematotoxicity 4° WHO (20/20 patients), requiring G-CSF for 16 ± 6 days. Nausea/vomiting started on day -4 with a maximum frequency on day +2 (20/20 patients, grade 2-3, mean grade 3 NCI). It persisted for 17 ± 5 days. Diarrhoea 3° (WHO) was seen in 19/20 patients starting on day -2 ± 3 days and continuing for 13 ± 9 days. Fever and rise of C-reaktive protein started on day +3 ± 3. Temperature > 38.5°C lasted 7 ± 6 days, antibiotics were used for 20 ± 10 days. Renal clearance went down to 50 % on average . The severest toxicities were mucositis 4°(WHO) (18/20 patients) starting on day 0 ± 3 and requiring up to 0.7 ± 0.4 mg/kg morphin hydrochloride for 16 ± 10 days. Pulmonary ventilation was necessary for 11 ± 5 days in 3 patients. 2 of those patients lost consciousness for 18.5 ± 5.5 days (neurocortical toxicity grade 4 NCI). Positive correlations could be demonstrated between the duration of vomiting and mucositis as well as for increasing age and the duration of diarrhoea. Preceding mIBG does not seem to influence the acute toxicity of the high dose regimen significantly.
Conclusion:

- **This schedule is tolerable. Therapy related death have not been seen. Main toxicities are haemotoxicity and mucositis. Neurocortical toxicity occurring in 10% up to grade 4 (NCI) is the severest toxicity.**
- **Future aims should address especially the mucositis in order to improve protocol tolerability.**

P-47

EFFECTIVE T CELL REGENERATION AFTER AUTOLOGOUS TRANSPLANTATION WITH CD34⁺ ENRICHED PERIPHERAL BLOOD MONONUCLEAR CELLS IN PRESCHOOL CHILDREN.

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Ex vivo enrichment of G-CSF stimulated peripheral blood mononuclear cells (PBMC) for the $CD34^+$ fraction results in effective T cell depletion. To test whether such T cell depletion would adversely affect T cell reconstitution after autologous stem cell therapy we monitored T cell recovery after high-dose chemotherapy rescued with autologous $CD34^+$ enriched PBMC ($CD34^+$ cell purity 70-90%, cell dose 4.8 to $6.5x10^6$/cells per kg BW) in three preschool children with stage IV malignant tumors (2 neuroblastoma, 1 rhabdomyosarcoma). Total T cells and T cell subsets were quantified by FACS. Two of the three cases achieved to reconstitute normal total ($CD3^+$) T cells (>1400/µl) within six months after treatment, in one case $CD3^+$ cells remained low (400/µl). The CD4:CD8 ratio, which at one month was inverse in two (0.2) and normal in one (1.1), returned to normal (≥1.5) by six months in all three cases. Effective T cell reconstitution in two cases occurred by a predominant expansion of $CD45RA^+$ cells in both, the $CD4^+$ and the $CD8^+$ subset (mean increase of $CD4^+/CD45RA^+$ cells 450-fold and of $CD8^+/CD45RA^+$ cells 14-fold, that of $CD4^+/CD45RO^+$ cells 7-fold and of $CD8^+/CD45RO^+$ cells ≤ 1-fold). As T cell CD45RA antigen expression designates naive, recently thymus-derived cells, this pattern of reconsitution might reflect high thymic activity in young patients. By these findings T cell recovery was similar to that observed in children after conventional chemotherapy or allogeneic BMT. The findings demonstrate that under conditions of (i) rescue with a high number of $CD34^+$ cells and (ii) young age T cell depletion is not predictive of delayed T cell recovery. Studies comparing T cell regeneration after stem cell therapy with and without T cell depletion are being undertaken.

P-48

IMMUNE RECONSTITUTION IN CHILDREN AFTER AUTOLOGOUS BONE MARROW TRANSPLANT

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Objective: We studied the kinetics of immune reconstitution in children undergoing autologous BMT.

Methods: Fifteen patients with neuroblastoma (NBL) received conditioning with high dose chemotherapy (VP-16, carboplatin, melphalan) and total body irradiation and had marrow purged with antibodies, and 15 patients with AML received chemotherapy (busulan, cyclophosphamide) and had marrow purged with 4-HC. Lymphocyte subsets, mitogen stimulation studies and serum immunoglobulins were studied every 4 months post BMT.
Results: There were only subtle differences between the 2 groups (AML vs NBL). Lymphocytes were reduced up to 4 months after BMT. CD2+cells were low at 12 months in 1/3 of patients. CD4+ cells was significantly depressed up to 8 months, with 1/3 of patients still low at 12 months. CD8+ cells recover rapidly post BMT and their levels were higher in patients who received TBI at 4 months. CD4+/CD8+ ratios remained below normal up to 8 months, mainly because of low CD4+ counts. CD3-CD16+CD56+ cells predominated in the early recovery phase and remained high even at 2 years in 2/3 of patients. CD20+ cells were elevated at least up to 12 months. CD45RO changed to CD45RA by 12 months. Median IgG levels were below the mean for age even after 2 years, and recover slower in children with NBL. IgA levels were below normal even at 24 months. IgM levels normalized at 12 months. Mitogen stimulation assays were markedly reduced at 4 months, but normalized by 8 months in most of the patients. Infections observed included catheter-related bacteremias and herpes-zoster reactivation.
Conclusions: Children have prolonged immunodeficiencies after autologous BMT, which are independent of underlying disease, conditioning and marrow purging.

P-49

AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR TREATMENT OF ISOLATED CENTRAL NERVOUS SYSTEM RELAPSE OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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The purpose of this study was to assess the role of ABMT in children with ALL who are in 2nd CR after an early isolated central nervous system (CNS) relapse. All children experiencing an isolated CNS relapse at 10 AIEOP-centers (Associazione Italiana Emato-Oncologia Pediatrica) from 1986 to 1992 were eligible for this study. The series included 69 patients relapsed within 3 years from diagnosis: 19 were given ABMT; 9 patients underwent ALLO-BMT from an HLA-identical sibling, and 41 received conventional chemotherapy (CHEMO). The comparison of the outcome after ABMT or chemo was performed using a Cox's regression model, adjusting for waiting time before transplantation and prognostic factors. The 5 years DFS was 56.3% (SE 12.3) for patients in the ABMT group. This compared favourably with the poor result [DFS 12.6% (SE 5.9)] obtained by the CHEMO group. The risk of failures was reduced by one-third in the ABMT group as compared to the CHEMO group in the multivariate analysis ($p<0.01$). This study suggests that ABMT may represent a valuable therapeutic choice with significant chances of prevention of further relapse, and eventually of cure, for patients in 2nd CR after an early isolated CNS relapse.

P-50

TOTAL BODY IRRADIATION, THIOTEPA AND CYCLOPHOSPHAMIDE AS CONDITIONING REGIMEN FOR CHILDREN WITH ALL GIVEN ALLOGENEIC BMT FROM HLA-IDENTICAL SIBLING

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Allogeneic bone marrow transplantation (BMT) from HLA-identical sibling can successfully treat children with acute lymphoblastic leukemia (ALL). However, as a significant proportion of patients with ALL and given BMT ultimately relapse, there is considerable opportunity for assessing the relative merits of different preparative regimens in the cure of these patients. To this purpose, we evaluated in a prospective study the safety, tolerability and anti-leukemic efficacy of a preparative regimen including total body irradiation (TBI), thiotepa (TT) and cyclophosphamide (CY) in patients with high-risk ALL in I complete remission (CR) (i.e. Ph+ positive, poor steroid response ALL with high tumor burden, T-cell immunephenotype and myeloid markers) and in II or III CR or with resistant disease. Thirty-nine children (24 males and 15 females, age range 2-17 years, median value 10 years) affected by ALL and given allogeneic BMT from HLA-identical siblings were conditioned with a combination of TBI (12 Gy in 6 divided fractions), TT (10 mg/kg) and Cy (120 mg/kg over 2 days). Donor marrow was infused on day 0, median nucleated marrow cell dose being 3.7 x 10^8/Kg (range 2.1 - 7.8). Graft-versus-host-disease (GVHD) prophylaxis consisted of Cyclosporine-A (Cs-A) administered intravenously at a dose of 1-3 mg/kg/day for the first 21 days and subsequently p.o. at a dose of 6 mg/kg/day for 4-6 months after transplant. All patients engrafted and the median time to achieve a sustained granulocyte count > 0.5 x 10^9/L was 11 days (range 7 to 23 days), whereas the median time for platelet engraftment (i.e. PLT > 50 x 10^9/L) was 23 days (range 12 to 50 days). The preparative regimen was tolerated without relevant toxicity. Incidence and severity of acute and chronic GVHD were 53% and 22%, respectively. Only one child died for grade IV acute GVHD. Nine patients (1 given BMT in 1st CR, 5 transplanted in 2nd CR, 1 in 3rd CR and 2 with resistant disease) relapsed at a median time of 6 months (range 3-10) after marrow transplant and this determined a cumulative probability of relapse of 27±8%. Twenty-nine out of 39 patients (74%) are alive and in continuous complete hematological remission with a median observation time of 17 months (range 6-56 months) and the projected event-free survival (EFS) at 3 years is 71±8%. The EFS of the 31 patients transplanted in 1st or 2nd CR is 73±8%, whereas the 8 patients given allogeneic BMT in more advanced disease had an EFS of 73±8%. In conclusion, these data suggest that TT is an effective cytotoxic drug that can be safely added to the classical TBI-Cy regimen. Due to its cell cycle independent action, good CNS diffusion and the limited extramedullary toxicity, TT may contribute to increase the percentage of children with ALL successfully cured by allogeneic BMT.

P-51

ROLE OF AN OBSERVATIONAL DATABASE IN CHILDREN GIVEN BONE MARROW TRANSPLANTATION

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Great improvements have been obtained in the treatment of childhood malignancies and currently about 2/3 of children with neoplasm can be cured. Bone marrow transplantation (BMT) has significantly contributed to the achievement of these results. Since 1985, the AIEOP BMT group has collected data concerning patients transplanted in 16 centers nationwide. All the data have been collected in a central database organized at the AIEOP Operation Office, within the AIEOP BMT Registry which is structurally integrated with other specific disease-oriented national databases. The Italian database includes information on 1602 transplants performed in 1487 patients, aged less than 17 years and updated to December 1995. Children were given either allogeneic BMT (alloBMT, 54% of the overall population) or autologous BMT (ABMT, 46% of the whole).The use of marrow and peripheral blood stem cell (PBSC) transplants constantly increased of about 12% per year. While in the period between 1985 and 1990 the number of ABMT amounted to about 60% of the total, in the last 5 years we observed a progressive increase of alloBMT which, in 1995, represented 66% of the total number of transplants. The majority of alloBMT were performed using an HLA-identical sibling as donor. However, the growing availability of HLA-typed volunteers has allowed an increasing use of matched unrelated donors (MUD), these donors having been employed in 5% of BMT in 1989 and in about 25% in 1995. Moreover, in the last few years, PBSC and cord blood have represented the source of hematopoietic stem cells in about 2% of alloBMT. It must be noted that, in the last 5 years, the use of PBSC has increased from 1% to 35% in children receiving ABMT. The most common indications of alloBMT and ABMT are different. In fact, among cases reported to the AIEOP-BMT Registry 58% of alloBMT were performed in patients with leukemia: 37% in ALL, 15% in AML, 6% in CML, respectively. In the remaining 42% of patients, transplants were performed for non-malignant disorders (35%), solid tumors (6%) and lymphoma (1%). On the contrary, the most common indications for ABMT were: leukemia in 47% of cases (24% ALL, 23% AML), solid tumors in 43% and lymphomas in 10% of patients. During the study period, the probability of 100-day mortality decreased constantly from 15% in 1985 to less than 10% and this value is particularly important considering the increasing use of matched unrelated volunteers. Advanced disease represented one of the most important factors influencing transplant-related mortality. Finally, an improvement in the overall 2-year event free survival post-BMT from a value of 40% in 1986 to more than 50% has been observed. The Registry database permitted the elaboration of several analyses on survival, relapse probability and transplant-related mortality for the different diseases. Moreover, study focusing on graft-versus-host disease, acute and late toxicities have been published. In conclusion, an exhaustive, reliable and updated database is a useful tool to obtain crucial information the role of BMT in children.

P-52

RESULTS OF HIGH DOSE CONSOLIDATION IN PATIENTS WITH LARGE CELLS ANAPLASTIC LYMPHOMA

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The prognosis of patients (pts) with large cells anaplastic lymphoma (LCAL) depends of initial presentation and response to treatment (Tt). Results of pts treated with high dose consolidation (HDC) for failure of first line protocols of the SFOP are presented.

Patients : between 1985 and 1996, 16 pts, 10 girls and 6 boys with a median age of 7 years (y) (range 2y-15y) received HDC. Murphy stage was II (4 pts), III (9 pts) and IV (3 pts). Ann Arbor stage was I (1 pt), II (3 pts), III (2 pts) and IV (10 pts).13 pts/16 had B symptoms at diagnosis.

Treatment : first line chemotherapy was COPAD (2 pts), HM89 (3 pts), HM91 protocol (10 pts) and VBVP with radiotherapy (1 pt). 15 pts were in complete remission (CR) at the end of this first Tt. Status at graft was CR2 for 10 pts, CR3 for 4 pts and primary or secondary refractory disease for 2 pts. Conditioning regimen was high dose chemotherapy alone for 10 pts (Busulfan containing in 6 pts) and chemotherapy associated with TBI in 6 pts. The hematologic rescue was autologous bone marrow in 9 pts and autologous peripheral blood stem cells in 7 pts.

Results :

- no toxic death was observed.
- 2 pts in progressive disease died at 1 and 10 m after graft.
- 8 pts relapsed at 1 to 18 m after the graft (median 10 m) ; 2 died at 1 and 7 m and 6/8 are alive at 0 to 24 m (median 18) after the end of Tt of the last relapse (1 pt received second HD CT) in RC 3 (4), RC 4 (1) or RC 5 (1).
- 6 pts are in continuing CR at 16 to 66m (median 33) after graft.
- results are not different in the TBI (3/6 relapses) and non TBI group (5/10).

Conclusions

1) Intensive treatment is not efficient in pts with progressive disease.
2) 1/3 of pts treated with HDC are alive in continuing CR after the graft.
3) New CR can be obtained in most of the patients relapsing following HDC
4) Therefore the necessity for HDC is questionnable in patients with a sensitive relapse.

P-53

TOXICITY AND INFECTIOUS COMPLICATIONS OF MEGATHERAPY (MGT) WITH AUTOLOGOUS PERIPHERAL STEM CELL REINFUSION (APSCR) IN CHILDREN WITH HIGH-RISK SOLID TUMORS. TEN YEARS OF SINGLE CENTER EXPERIENCE

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Aim of the Study: Megatherapy consisting of high-dose cytotoxic drugs with or without total body irradiation (TBI) followed by autologous PBSC support is increasingly used in children with bad-prognosis solid tumors. Still, the impact of this therapy is a matter of much debate. The purpose of this study was to evaluate toxicity, infectious complications and outcome in a cohort of pediatric patients with high-risk solid tumors receiving different MGT approaches in the same center.

Patients and Methods: From July 1987 to March1997, a total of 44 patients (pts) (23 males and 21 females), with a median age of 12,7 years (range 1,1-26,1) underwent 60 courses of MGT. Diagnosis was neuroblastoma in 18 pts, Ewing's sarcoma and primitive neuroectodermal tumor in 18 pts, rhabdomyosarcoma in 6 pts and osteosarcoma in 2 pts. The median observation time is 2,1 years (range 0,1-9,6). MGT with TBI was implemented in 18 pts while MGT consisting of cytotoxic drugs only was used in 26 pts. Out of the latter group 13 pts were treated with repetitive , i.e 2 to 3 courses, of MGT. The dose of stem cell support increased over the years: While in the early years only chemotherapy (CHT) mobilized stem cells were used, more recent pts were stimulated with G-CSF after CHT in addition, resulting easily in harvests of 20 to 30 $x10^6$ CD34 positive cells/ kg body weight and allowing thus PSCR of at least $5x10^6$CD34 positive cells per cycle for recent repetitive courses.

Results: The overall survival at the median observation time was 32% for the whole group. Evaluation of engraftment parameters showed significantly better results for children treated with MGT without TBI. This group of children had also statistically significant less toxicity and infectious complications as measured by incidence and severity of mucositis, days with fever, days with antimicrobial agents i.v., maximal CRP, days of elevated CRP values and days in hospital. In the TBI group 3/18 patients died of toxic and infectious complications and only 2/26 in the non-TBI group.The toxic death rate for both groups was thus 16,7% and 7,7%, respectively. No differences between first and repeated episodes of MGT with regard to engraftment parameters, toxicity and infectious complications were found.

Conclusions: These data show that non TBI repetitive MGT regimens have an acceptable rate of toxic and infectious complications with adequate amounts of PSC support and might improve prognosis of high-risk solid tumors on the bases of increased dose intensity.

P-54

ALLOGENEIC BMT IN SECOND REMISSION OF CHILDHOOD ALL, A CASE CONTROL STUDY.

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There are no randomised studies comparing allogeneic BMT and chemotherapy in second remission (CR2) of childhood ALL. This is a case control study of all 76 Nordic children allografted in CR2 of ALL with a matched family donor between 6/81 and 1/95.

For each BMT case two children in CR2 treated with chemotherapy (controls) were selected who matched these criteria: 1) time of dx, 2) T v. non-T ALL, 3) site of relapse, 4) initial risk group, 5) sex and 6) relapse < or ≥ 6 months after cessation of therapy and 7) length of CR2 in control ≥ time from relapse to BMT in case + 2 months.

Results: 152 patients who mathed the criteria could be selected from the data base. 2.p-EFS was 0.41 for 76 BMT cases and 0.21 for 152 matched controls (p=0.02) with no difference between the first and second half of the study period. 2.p-EFS for case/controls was 0.59/0.28 in girls (p=0.03) and 0.30/0.18 in boys (p=0.2). When compared with boys girls had a higher 2.p-EFS (0.59 v 0.30). Survival after bone marrow relapse was significantly higher for cases than for controls (0.36 v 0.14, p=0.005), but there was no difference in children with extramedullary relapse. There was no significant difference in survival after BMT for early compared with late first relapse, although the survival was higher for the BMT group.

Conclusions: In this study of BMT in 76 children with relapsed ALL BMT was correlated to a better over all prognosis (p=0.02) especially in BM relapses (p=0.005) and in girls (p=0.03) when compared with 152 matched controls. Survival was similar after BMT for early and late relapses.

P-55

AN UPFRONT PHASE II WINDOW OF IDARUBICIN IN THE TREATMENT OF EXTRAOCULAR RETINOBLASTOMA. PRELIMINARY RESULTS

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Background and objectives: Metastatic retinoblastoma is seldom curable with conventional chemotherapy and the identification of newer potentially active drugs is essential to improve its outcome. Doxorubicin is used for retinoblastoma. However, there are no data about its activity as a single agent in retinoblastoma and the major drawbacks for its use are its cardiotoxicity and its poor penetration to the CNS. Idarubicin and its metabolite Idarubicinol may be less cardiotoxic and have a better penetration to the CNS. This study was designed to test the response rate to an upfront window of Idarubicin in patients with extraocular retinoblastoma.

Patients and Methods: From October 1995 to December 1996, 5 patients with biopsy-proven extraocular retinoblastoma were included in this study after informed consent. All had metastatic or orbital disease. They received 2 cycles of Idarubicin (15 mg/m^2/dose in a 30-60 minutes infusion on days 1 and 2), 3 weeks apart. Response was evaluated 3 weeks after the 2nd cycle.

Results: Five patients were included (3 bilateral). 1 patient achieved a complete remission of an orbital mass, 3 patients had partial response (in one of them a contralateral intraocular tumor had signs of regression consisting in calcification and marked decrease in size including vitreous seeds) and 1 patient had a mixed response (complete response in the orbit and bone marrow, partial response in the contralateral orbit and progressive disease in the CNS).
Toxicity was mainly hematological. Grade IV hematological toxicity developed after all cycles. Documented infections occurred in half of the courses. Median duration of neutropenia (ANC<500/mm^3)was 10 days. No echocardiographic changes were recorded. No other grade III/IV toxicity occurred.
Conclusions: In this preliminary series, Idarubicin proved to be highly active for extraocular retinoblastoma with a 80% response rate, however more patients must be accrued to make definitive conclusions.The only case with intraocular disease that could be evaluated, also had a promising response. Hematological toxicity is severe but manageable.

P-56

VINCRISTINE PHARMACOKINETICS IN RELATION TO CLINICAL NEUROPATHY.

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We prospectively studied the relationship between vincristine pharmacokinetics and clinical neuropathy. Peripheral neuropathy is the dose limiting toxicity of vincristine. Data on vincristine pharmacokinetics in children are scarce and the relationship between pharmacokinetic parameters and clinical neurotoxicity has been described in only one retrospective study.
Newly diagnosed children (n = 14) with acute lymphoblastic leukemia (ALL) or non-Hodgkin's lymphoma (age: 2 -16y, sex: m=9, f=5), admitted to our hospital between November 1994 and November 1996, treated according to the Dutch Childhood Leukemia Study Group ALL-8 protocol, were enrolled into the study. Clinical neuropathy was scored according to a modified WHO score at diagnosis and one week after the first four weekly vincristine i.v. bolus administrations (1.5 mg/m2, max 2.5 mg). Vincristine plasma concentrations were measured by HPLC with electrochemical detection. A two compartment model was fitted to the data using the ADAPT II program with a Bayesian parameter estimation method. Cumulative area under the concentration-time curves (AUC) and simulated peak concentrations at 1 min were related to neurotoxicity scores.
We were unable to find a significant relationship between the cumulative AUC after the first four vincristine administrations and neurotoxicity. However, preliminary data suggest that higher vincristine peak concentrations result in a higher degree of neurotoxicity. These results suggest that avoiding high vincristine peak concentrations, by use of continuous infusions, might decrease vincristine neurotoxicity.
Obviously, a negative influence on efficacy should be ruled out.

P-57

ROLE OF FOLYLPOLYGLUTAMATE SYNTHETASE (FPGS) AND FOLYLPOLYGLUTAMATE HYDROLASE (FPGH) IN METHOTREXATE RESISTANCE IN ACUTE MYELOID AND RELAPSED LYMPHATIC LEUKEMIA

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Objective: Intracellular polyglutamylation of MTX is an essential step for the antileukemic activity of this drug because it increases its retention and K_i, and other enzymes can be inhibited besides the main target enzyme dihydrofolate reductase. FPGS catalyses the formation and FPGH the breakdown of MTX polyglutamates. Little is known about possible polyglutamation defects in relapsed ALL (rALL); Polyglutamylation defects were associated with the intrinsic MTX resistance in AML, but the exact cause of this defect in AML is unknown. This study aims to investigate MTX polyglutamation defects and its causes in AML and in relapsed ALL.
Methods and Results: The median accumulation of long chain polyglutamates (MTX-Glu_{4-6}), after 24 hr *in vitro* exposure to 1 μM ^{3}H-MTX, was 4-fold higher in leukemic cells from 29 initial ALL patients compared to 5 rALL and 9 AML patients (850, 230 and 190 pmol/10^9cells respectively). The activity of FPGS was similar in leukemic blasts for 23 initial ALL and 6 relapsed ALL patients, but 3-fold lower in 11 AML patients: 0.93, 0.87 and 0.33 nmol of MTX-[^{3}H]Glu_2 formed/hr/mg protein, respectively. FPGH was 2-fold lower in leukemic cells from 71 ALL vs 16 relapsed ALL and 25 AML patients: 17.7, 31.2 and 37.8 nmol MTX-Glu_2 hydrolysed/hr/mg protein.
Conclusions: Both AML and relapsed ALL show defects in accumulation of long-chain MTX polyglutamates, but it should be taken into account that especially the number of relapsed ALL cases is limited. In AML, this defect is associated with a decreased formation of polyglutamates by a low FPGS activity as well as with increased breakdown of polyglutamates by a high FPGH activity. In relapsed ALL, the breakdown by a high FPGH activity plays a role but the decreased formation does not seem to be important in this small number of cases because the FPGS activity was similar to that in untreated ALL.
(Supported by the Dutch Cancer Society, grant 94-679)

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THE USE OF SAMARIUM-153-EDTMP IN THE TREATMENT OF PEDIATRIC SKELETAL MALIGNANCIES: A PHASE I TRIAL

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Samarium-153-ethylenediamine tetramethylene phosphonic acid (EDTMP) is a bone-seeking radiopharmaceutical that concentrates preferentially in pathological bone. Sm-153-EDTMP was given to 7 children age 5-26 years (median, 10) with bony metastases. The histological diagnoses were: neuroblastoma-4, osteosarcoma-2, medulloblastoma-1. All children had previous chemotherapy and 3 had radiotherapy. Two patients(pts) had Sm-153-EDTMP before high dose chemotherapy (HDCT). Sm-153-EDTMP, in dose escalation, was injected as a single intravenous dose in 6 children and in repeated doses in one pt. Two children had 4 treatments with 1.0 mCi/kg (37 MBq), 5 with 1.5 mCi/kg and one with 2.0 mCi/kg. The only toxicity observed was hematological. In 8 treatments, without HDCT, the median nadir platelet count was 26,000/mm3 (range, 5,000-106,000). The median platelet nadir was Day 32 (range, 21-40). The median duration of thrombocytopenia (<50,000/mm3) was 20 days (range, 0-22). The median nadir neutrophil count was 1386/mm3 (range, 882-2701). The median neutrophil nadir was Day 28 (range, 24-40). Hematological recovery was complete in all children. Although the number of children treated with Sm-153-EDTMP is small, these results suggest that it can be given safely to children with bony metastases. Further larger studies are needed to determine the role of Sm-153-EDTMP in pediatric oncology.

P-59

A PHASE II STUDY OF BUSULFAN IN CHILDHOOD MEDULLOBLASTOMA/PNET.

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Busulfan is the alkylating agent frequently included in bone marrow transplantation programs for children as a component of myeloablative and antineoplastic therapy. It is being used as a preoperative regimen at high dosage both for allogeneic bone marrow transplantation and autologous bone marrow transplantation (ABMT) in solid tumors, in particular brain tumors. However, no studies are reported in humans about the busulfan efficacy as a single agent at "standard" dosage. This phase II study was performed in order to evaluate the antitumor activity of busulfan in children with relapsed medulloblastoma/PNET with progressive disease. Ten children aged between 2 and 18 years (median 7 years), 7 males and 3 females, have been treated. Busulfan was given orally at dosage of 200 mg/m^2 administered over 2 days. Tumor response was assessed by magnetic resonance imaging 4 to 5 weeks later. If no progression was observed, busulfan was given orally again (100 mg/m^2/day x 4 d) followed by thiotepa (200 mg/m^2 i.v. x 3 d). Cryopreserved bone marrow or peripheral stem cells were reinfused 48 h after completion of chemotherapy. Following the administration of busulfan alone 5 objective responses (4 PR, 1 MR) were observed; 4 patients showed a stable disease and in 1 patient there was a progressive disease. Following ABMT in responsive patients, further tumor reduction was noted. After busulfan as a single agent at "standard" dosage only hematological toxicity was observed (neutropenia and thrombocytopenia grade II-IV WHO). This study, although preliminary, showed that busulfan as a single agent has therapeutic effect in relapsed pediatric MB/PNET at lower dosage as compared to the doses employed with ABMT. These results justify the use of busulfan in high dose chemotherapy regimens in relapsed patients with MB/PNET, followed by ABMT.
Supported by A.I.R.C.

P-60

TAXOL IN RESISTANT OR RELAPSED PEDIATRIC MALIGNANCIES: 435 mg/m^2/COURSE IN A Q4D REGIMEN IS A SAFE DOSE

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A previous phase I-II study (presented at the Vienna SIOP meeting in 1996) reported on 26 pediatric pts, treated with Taxol at escalating dosages, according to a 4-day, fractionated brief infusional schedule (Q4D regimen), adopted after Helson L. had suggested (basing on in-vitro tumor cell kinetics studies) its greater efficacy as compared with the traditional 24-hour infusion given every 21 days (Q21D regimen).
Starting at 60 mg/m^2/dose infused over 90 minutes at days 1, 5 and 9 (Q4D, total dose 180 mg/m^2/course), we repeated courses every 21 days; pts were evaluated after 3 courses (9 doses) or in case of clinically evident disease progression. We increased dose by 15 mg/m^2/dose (45 mg/m^2/course) at each dose level; after reaching 135 mg/m^2/dose (405 mg/m^2/course), doses are being increased in 10 mg/m^2/dose increments. 10 pts were treated at the 60 mg/m^2/dose level, 3 at 75 mg, 7 at 90 mg, 6 at 105 mg, 3 at 120 mg and 3 at 135 mg (total dose 405 mg/m^2/course). A total of 32 pretreated pts with resistant or relapsed tumors, median age 6 years (range 0.3-17 years), have been hitherto treated: 7 neuroblastomas, 5 CNS tumors, 5 rhabdomyosarcomas, 5 Ewing's sarcomas, 2 PNET, 2 Wilms' tumors, 2 osteosarcomas, 1 hepatocarcinoma, 1 retinoblastoma, 1 germ cell tumor, 1 congenital leukemia.
30/32 pts are evaluable for response (1 pt at the 60 mg/m^2/dose level and 1 pt at the 75 mg/m^2/dose level dropped out because of PD). All 32 treated pts were evaluated for toxicity, even if they had not completed treatment; hematopoietic growth factors were not administered in this study. The following responses were recorded in the 30 evaluable pts at different dose levels: no CR; 3 PR (10%) in pts with retinoblastoma, rhabdomyosarcoma and Ewing's sarcoma; 5 MR (16.6%) in pts with brain tumors (2), rhabdomyosarcoma, Ewing's sarcoma and congenital leukemia; 8 SD (26.6%) and 14 PD (46.6%). Hypercholesterolemia and hypertriglyceridemia were recorded in 32/32 pts (100%), dermatitis in 12 (38%), skin rash in 4 (13%), anemia in 5 (16%), thrombocytopenia in 5 (16%), leukopenia in 4 (13%), diarrhea in 2 (6%) and neuropathy in 1 pt (3%). All toxicities were less or equal to ECOG grade 2. Nausea and vomiting, FUO, cardiac, renal and hepatic toxicities were not observed. We have furthermore treated 5 pts at the 145 mg/m^2/dose level (total dose 435 mg/m^2/course); 3 pts were withdrawn from the study by their parents, 1 pt is TETE and 1 SD was recorded in the one evaluable pt (neuroblastoma). No new untoward side effects have emerged, and we are looking forward to further escalating the dose, as the maximum tolerated dose is still to be determined. *(Supported in part by Bristol-Myers Squibb grant CA 139-219)*

P-61

MEDULLOBLASTOMA STAGING: IS THE CEREBROSPINAL FLUID CYTOLOGY A RELIABLE PROGNOSTIC FACTOR?.

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Although the presence of metastases in the neuraxis at the time of diagnosis is probably the most important factor predicting for survival in children with medulloblastoma, there is no wide agreement in the predictive value of a positive ("+") cerebrospinal fluid (CSF) cytology. It has also been suggested that a postoperative "+" CSF cytology may be the result of surgical shedding and therefore a false "+". We analyzed 86 medulloblastoma patients (pts) (age: 8.2 years, median) treated between 1972-1991. All pts completed surgery and craniospinal axis irradiation. A thorough retrospective investigation was performed aiming to get optimal information concerning the extension of the disease in the neuraxis (i.e., pre and/or postoperative CSF cytology, myelography, CT, MRI). From 54 pts coded as "non metastatic" (M0) in the Swiss pediatric tumor registry, documentation of negative ("-") CSF cytology was found in only 39. The remaining 15 pts were restaged as Mx. Thirteen pts were M1 ("+" cytology); 17, M2 (gross cerebral or cerebellar subarachnoidal invasion); and 2, M3 (gross subarachnoidal spinal seeding). Fifty-two pts were staged on cytologic grounds exclusively (M0 or M1). Myelography and/or spinal MRI were performed in only 2/53 pts before 1986, but in 20/33 thereafter. Five and 10-year overall survival figures were respectively, 76 and 54% for M0, 68 and 50% for Mx, 36 and 25% for M1, and 22 and 22% for M2+3 pts (p=0.0004). No significant survival differences were observed between M1 and M2+3 pts (p=NS). Among 26 pts with only postoperative CSF studies, 7 were "+". Their outcome was similar to 6 preoperatively staged M1 pts and significantly different from M0 pts (p=0.0012). In 14 pts both pre- and postoperative CSF cytology was performed. Total agreement was observed between the pre- and postoperative results (6 "+" and 8 "-"). Among the 19 M2+3 pts CSF cytology was "-" in 8, "+" in 5, and unknown in 6. In summary, a "+" CSF cytology either pre- or postoperatively predicts for a poor outcome (similar to stage M2+3). A postoperative cytology reproduces the results and survival of preoperatively staged pts and, if "+", should not be considered a simple surgical artifact. A "-" cytology does not exclude, however, a more advanced stage (M2 or M3).

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FAMILIAL CASTLEMAN'S-LIKE DISEASE: POSSIBLE LINK TO KAPOSI'S SARCOMA ASSOCIATED HERPESVIRUS [HUMAN HERPES VIRUS 8] (KSHV/HHV-8)

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Objective: To report early childhood occurrence of giant lymph node hyperplasia resembling Castleman's disease (CD) in a woman and her three children.
Methods: History, physical findings, laboratory results and clinical course of the patients were described.
Results: The mother and two daughters (the oldest is a half-sister to the younger siblings) presented with obstructive upper airway symptoms in the first year of

life. The youngest patient , 1 1/2-year-old boy is asymptomatic. Enlarged hilar and mediastinal lymph nodes were detected radiologically in all four but developed additional abdominal and/or pelvic lymphadenopathies in the children. Axillary lymph node biopsy in the mother and mediastinal node biopsies in the two older siblings showed lymphoid hyperplasia resembling hyaline vascular type of CD. The mother was treated with local irradiation with the complete resolution of the thoracic mass. Both sisters had remained unresponsive to steroid treatment but upper airway symptoms resolved spontaneously over time. The older sister continues to have mediastinal lymphadenopathy with some decrease in size at age ten. The younger sister has a stable thoracic disease at age four but developed pelvic masses coinciding with a recent EBV seroconversion with persistent high-titers. Pelvic lymph node biopsy showed same pathology as above and PCR analysis showed KSHV/HHV-8 DNA sequences. The oldest sibling's peripheral blood lymphocytes were positive for the KSHV/HHV-8 DNA as well. Both the parents and the siblings are HIV negative. Studies for a possible underlying immune dysfunction and mechanisms of vertical transmission are in progress.

Conclusions: Familial occurrence of multicentric Castleman's-like disease with positive KSHV/HHV-8 suggested a viral etiology possibly associated with an inherited aberrant immune response.

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MYELOFIBROSIS IN HODGKIN'S DISEASE

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Myelofibrosis, secondary to Hodgkin's Disease (HD) is very rare in children. There is only an isolated case report of myelofibrosis in a child with H.D. We present 4 children with HD who had myelofibrosis with pancytopenia either at presentation or developed following chemotherapy. Case 1) A 10 yr old boy presented with generalised lymphadenopathy, hepatosplenomegaly, ascites and severe anemia. Bone marrow biopsy showed myelofibrosis. Lymph Node (LN) biopsy demonstrated HD. The child received 4 cycles of COPP when he developed marked pancytopenia and died due to sepsis. (2) A 10 yr old boy presented with generalised lymphadenopathy, hepatosplenomegaly, jaundice, and pancytopenia. LN biopsy showed H.D. He received 5 cycles of COPP and was admitted after 5th cycle with febrile neutropenia. Bone marrow biopsy revealed extensive fibrosis. Chemotherapy had to be discontinued because of severe pancytopenia. He succumed to infection. (3) A 12 yr old boy was diagnosed HD at 6 yrs of age and treated with 8 cycles of COPP, presented with fever, jaundice, anasarca, generalised lymphadenopathy, hepatosplenomegaly, anemia and leukopenia. LN biopsy showed relapse HD. He died of hepatic failure. (4) An 8 yr old girl was admitted with cervical lymphadenopathy, hepatosplenomegaly and pancytopenia. LN biopsy showed HD. Bone marrow biopsy showed fibrosis with RS cells. She has just completed 3 cycles each of COPP/ABVD. All 4 patients had HD of mixed cellularity type with B symptoms. We emphasize that myelofibrosis with pancytopenia may be a manifestation of H.D. It poses a problem in management and has a poor outcome.

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ANALYSIS OF LONG-TERM SEQUELAE IN 105 PATIENTS (pts) TREATED FOR MEDULLOBLASTOMA IN CHILDHOOD BY COMBINED THERAPY IN A SINGLE INSTITUTION

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Objectives : The aim of this study was to record long-term sequelae in children who survived 5 years (y) after diagnosis.

Patients and methods : We reviewed the files of 105 pts treated for posterior fossa (PF) medulloblastoma (102) and PNET(3) hospitalized between 1964 and 1991. The mean follow up period of these pts was 11 y. (5-30). The mean age was 7 y (0-19 y) at diagnosis and 19 y at evaluation. There were 65 boys and 40 girls. All pts were operated and received post operative irradiation : 50 - 55 Gy to PF and prophylactic cranio spinal irradiation (25 Gy in 30 cases, 35 Gy in 72 cases), 83 pts also received adjuvant chemotherapy.

Results : 10 relapses occurred. 7/10 pts died of progressive tumor. We observed the usual sequelae of endocrine and growth function : (short stature < 3SD : 31 pts, obesity : 11 pts, thyroïd deficiency : 25 pts) 2 of the 50 pts treated by GH developped a Creutzfeld-Jacob disease.

72 neurological abnormalities were recorded. Among them, 15 cases of severe epilepsy (1 pt died because of status epilepticus). Hearing loss (27 pts) and visual deficiency (43 pts) were observed. Neuropsychological function ranged from normal to impaired. 28 pts never had reading acquisition. Among the 66 pts older than 18 y at evaluation, only 13 had a normal job, 11 a driver's licence, 7 their own apartment and 5 got married. 4 pts presented a post transfusional hepatitis C. 10 pts developped a second tumor and 2 of them died (AML, glioblastoma). 1 of the 11 deaths was due to a car accident.

Conclusion : The study of outcome of children treated for medulloblastoma shows a high percentage of late endocrine and neuropsychological sequelaes.

Early testing may define pre-existing deficiency and appropriate academic interventions might improve this poor outcome.

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FINE NEEDLE ASPIRATION BIOPSY IN SUPERFICIAL LYMPHNODES: EXPERIENCE FROM A SINGLE INSTITUTION

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The experience achieved using fine needle aspiration biopsy (FNAB) on lesions involving the superficial lymphnodes (LN) is described. From June 1988 to December 1996, 214 pts (100 F, 114 M, age 6-180 months-med 66 m) with peripheral lymphadenopathy had 234 FNABs on the following LN: 106 cervical, 37 submandibular, 32 axillary, 28 inguinal, 9 supraclavicular, 8 retro-preauricolar, 8 parotideal, 3 occipital, 3 paramammary. After the application of an anesthetic ointment, the exam included the use of 22-25 gauge needles with full suction. The smears were stained according to May-Grunwald Giemsa or Papanicolau. During the last 3 years 35 cases had an echoguided procedure.

Results. In 196/234 FNABs a non tumoral lesion was found: 50 suppurative, 34 chronic and 114 non specific-reactive lymphadenitis were diagnosed. A malignant lesion was found in 19/234 cases: 9 HL, 5 NHL, 1 LLA, 3 metastases of RMS, 1 metastasis of nasopharyngeal carcinoma. In 11/234 lesions, suspicious of malignancy at FNAB, the surgical biopsy confirmed the diagnosis. The remaining 8/234 aspirates were not adeguate to achieve a cytologic diagnosis. No complications were observed. The sensitivity was 99% (2 false negative). The specificity was 97% (8 false positive).

Our data confirm that FNAB is a simple, accurate and well tolerated method in the initial diagnostic approach of enlarged lymphnodes in children.

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FAMILIAL HODGKIN.

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Familial Hodgkin is a well defined entity with one or more members from the same family to be affected. In most of the studied cases there is a lack of EBV association while in Hodgkin's disease generally there has been an established correlation with EBV genome. Two cases of familial Hodgkin's disease are described. The first concerns a boy 12 years old, with left cervical lymphadenopathy, biopsy positive for mixed cellularity Hodgkin's disease and clinical, laboratory staging IIIA. His grandfather of maternal origin has been diagnosed with nodular sclerosis Hodgkin's disease stage IIIA, 10 years ago. The second concerns a boy 10 years old with cervical lymph notes biopsy proven to be nodullar sclerosis Hodgkin's disease stage IIIA. In this boy 10 years ago and while his mother was at the 4th month of pregnancy, his father has been diagnosed for nodular sclerosis Hodgkin's disease stage IA from biopsy of left inguinal lymph node. Lymph modes from both cases described showed the presence of EBV (EBER and LMP with in situ hybridization and immunohistochemistry). The occurrence of familial Hodgkin's disease and its correlation with Epstein Barr virus in our cases as well as to the existing literature are commended.

P-67

PROGNOSTIC VALUE OF IMMUNOHISTOCHEMICALLY DETECTED CD44 ISOFORMS EXPRESSION IN PATIENTS WITH NEUROBLASTOMA.

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BACKGROUND. The human CD44 cell surface glycoprotein has been known to be involved in a variety of functions including lymphocyte homing, extracellular cell matrix attachment and tumor metastasis. Overexpression of alternatively spliced CD44 isoforms (CD44v) has been reported to correlate with poor prognosis in several human malignancies. On the other hand, in neuroblastoma (NB), the overexpression of CD44 standard form(CD44H) has been reported to strongly correlate with good prognosis. However, to the authors' knowledge, there are no studies concerning the prognostic value of CD44v overexpression in patients with NB.

METHOD. Sixty-five cases of NB were examined immunohistochemically for overexpression of CD44H and CD44v. Four different murine monoclonal antibodies to CD44H and CD44v containing variant exons v5, v6, v7-8 were used. The correlations of CD44 overexpression with clincal stages, ages (more than 1y or not), and disease free survival (DFS) were investigated.

RESULTS. The expression of CD44H, CD44v5, CD44v6, CD44v7-8 were detected in 51% (33/65), 65% (42/65), 71% (46/65) and 0% of specimens, respectively. Expression of CD44H positively correlates with favorable clinical stages and younger age. Whereas, expression of isoforms had no correlation with clinical stages or age. DFS did not correlate with CD44 overexpression.

CONCLUSION. Immunohistochemically detected overexpression of CD44 isoforms is not correlated with prognosis in patients with neuroblastoma.

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ABDOMINAL NON-HODGKIN'S LYMPHOMA; A REVIEW OF 75 CASES

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The aim of this retrospective study was to evaluate the role of surgery, the pattern of treatment failure and the site of relapse in abdominal Non-Hodgkin's(NHL) Lymphoma.

154 children with NHL presented to Cairo University Children Hospital over a 5-years period (1991 through 1995). 75 patients(48.7%) were found to have primary abdominal NHL. All patients presented with symptoms suggestive of intestinal obstruction, with a mean period of 2-3 months before diagnosis. Sixty four patients(85%) were subjected to laparotomy. Treatment protocols were tailored according to the extent of resection and histo-pathologic subtypes.

Complete surgical excision with no macroscopic residual disease could be achieved in 38 patients(51%). Maintained complete remission rate on combination chemotherapy was 84.4% for complete excision,64.7% for partial and 62% for patients who had biopsy taken only. The difference was not statistically significant. The five years overall actual survival for the whole group was 55%. Patients who had limited, completely resected disease had a statistically significant higher survival (91%) than the other two groups(72%,28%,p<0.01). Three patients developed extra-abdominal relapse in spite of complete surgical excision and post-operative combination chemotherapy.

The study suggests that complete surgical excision significantly increases the survival of limited abdominalNHL However, extra-abdominal relapse may still occur despite complete surgical excision and combination chemotherapy.

P-69

CURRENT PAEDIATRIC SURGICAL APPROACH TO HODGKIN'S LYMPHOMA

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Introduction: Since Glaststein performed splenectomy to establish Hodgkin's lymphoma (HL) staging, the role of paediatric surgeons has decreased. The aim of this study was to review our surgical approach since 1984. ***Material and Methods:*** The clinical histories of 47 children (29 boys, 18 girls; age range: 4-15 years; mean age: 10 years) diagnosed of HL (11 cervical, 7 mediastinal and 7 combined) at our centre between 1984 and 1996 were studied. Tumours were 12 stage IA, 10 IIA, 10 IIB, 5 IIIA, 6 IIIB and 3 stage IV. Pathologic study revealed nodular sclerosis in 29 patients, mixed cells in 9 and lymphocytic predominance in 7. Diagnosis was established by lymph node biopsy, particularly in cervical location, either by PAAF or CT-guided. Only in 2 patients was splenectomy performed for staging. Another patient was reoperated on years later when pulmonary superior lobectomy was performed. A further patient recently underwent laparoscopic surgery to resituate both ovaries to protect them from radiotherapy side effects. All 47 children were treated by a combination of chemotherapy and radiotherapy (low doses 20-45 Gy). ***Results***: Two patients died of respiratory distress and aplasia post-

chemotherapy (poor responders). Both were stage IIB with cervical location. The remaining 45 patients are alive and in complete remission. Recurrence in two of these required change in their chemotherapeutic strategy. ***Conclusions***: At present, early diagnosis by closed and, on few occasions, open biopsy, clear imaging techniques and combined chemotherapy and radiotherapy yields very good results and distances the paediatric surgeon from bygone splenectomies and liver biopsies. The current approach should be reserved for scarce lymph node biopsies and ovarian protection by laparoscopy.

P-70

EXPERIENCE WITH INTRA-ABDOMINAL NON-HODGKIN'S LYMPHOMA: Role of Surgery

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Objective: Children presenting with intra-abdominal non-Hodgkin's lymphoma (NHL) are usually referred to the surgeon because they often complain of abdominal pain or palpable mass. We report nine such patients with intra-abdominal NHL in order to focus on the most appropriate surgical procedure for one of the most rapidly growing cancers in children.

Subjects: The patients ranged in age from 1- 16 yr, comprised 4 males and 5 females. Five of the NHLs involved small or large intestine, of which 2 tumors had caused intussusception at the disease onset. Three other intestinal NHLs each formed a huge mass, causing a considerable degree of bowel obstruction. The primary foci in the other cases were ovary and pancreas in one case each, one case had diffuse pelvic involvement, and one showed widespread retroperitoneal infiltration.

Results: All patients underwent abdominal exploration. Three children with huge masses or widespread disease underwent only biopsy of the tumor, and 6 patients underwent mass resection. All patients except one received chemo- and radiotherapy. A 1 year-old baby girl suffering from intra-abdominal expansion of the disease died soon after surgery. Three other children died due to tumor recurrence after extensive chemo- and radiotherapy. Survival of the patients was achieved only when the masses could be resected primarily, or when a full dose of anti-cancer chemotherapy and radiotherapy was given with stem cell transplantation.

Conclusion: Surgery for NHL in the abdomen should be designed to remove as much lymphomatous tissue as possible. When there is residual disease after initial surgery, a second look procedure after chemotherapy is recommended since extensive surgical procedures induce major complications and may delay the primary postoperative treatment.

P-71

Multidisciplinary approach to Wilms tumor -18-years of experience

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From January 1978 to December 1996, 106 patients with Wilms Tumor (WT) were diagnosed. Of these 106 patients, 61 (% 58) were male and 45 (% 42) were female (M/F= 1,35); the median age at diagnosis was 39 months (Range 2-144 months). The most frequent presenting findings included palpable mass (% 95), abdominal pain (% 31) and macroscopic himaturia (% 6). Associated malformations were present in 3 patients (% 2.8): macroglossia, hypospadias and aniridia. Distant metastases were found in 10 cases (Lungs:5, liver:3, bone:1, brain:1). Four of the tumors were bilateral. Atrial trombosis was found in 1 case. As surgical treatment nephrectomy (50 left, 42 right) was performed in 92 patients, partial nephrectomy in 4 cases and only biopsy in 10 cases. In bilateral WT cases tumorectomy was performed with or without nephrectomy. The distribution of the 106 patients according to clinical stage was: 11 stage I (% 10), 44 stage II (% 42), 37 stage III (% 35), 10 stage IV (% 9) and 4 stage V (% 4). Histologically, 102 of the cases were evaluable: favourable histology (FH) was diagnosed in 90 (%88.2) and unfavourable histology (UF) in 12 patients (% 11.8). Tumor relapse was seen in 20/99 patients (% 20): 2 in stage I, 5 in stage II, 7 in stage III, 4 in stage IV, and 2 in stage V. Regarding histology, 15 of patients with FH (% 16.6) and 5 patients with UF (% 41.6) relapsed. Ninety-one patients were treated according to NWTS and 8 patients according to SIOP protocols. Seven of the patients were followed in other centers. The EFS and overall survival rates at 2 years are % 71.6 and % 79 respectively. The ESF and overall survival rates at 5 years are % 67.6 and % 71.8 respectively.

P-72

TEN YEARS' EXPERIENCE WITH HEPATOBLASTOMA IN POLAND 1985 - 1995.

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Between 1985 and 1995 fifty three patients with hepatoblastoma were treated . 49 were suitable for retrospective analysis to evaluate treatment efficacy and prognostic factors. Median age was 2,5 yrs and boys preavailed 34:15 (69%). In 39% of cases the tumor involved both liver lobes and 39% of tumors were multifocal. 14% of pts. presented with metastases at diagnosis and in 23% extrahepatic tumor extension or lymph nodes involvement were found. Different chemotherapy protocols based on cisplatin, doxorubicin, carboplatin, ifosfamid, VP-16 and 5-FU were applied. Induction chemotherapy was used in 24 pts. (49%) and in 17 of them (71%) tumor response was achieved. 27 pts. underwent surgical tumor removal (55%). 22 pts. survived and median follow-up time is 58 mo. (45% survival). 17 are in I remission, 2 in II remission and 3 are alived with disease. Interestingly 3 survivors were cured by chemotherapy alone. Median survival of dead pts. was 11 mo. 70% of them have never been operable. Much bigger proportion of patients receiving neoadjuvant chemotherapy in the survivors group (73% vs. 30%) calls attention. Probably it was introduction of an effective induction chemotherapy, which changed the outcome of many pts., making their tumors operable. Definite surgery was feasible in 86% of survivors vs. 30% of dead pts. In the induction chemotherapy group survival was 66% vs. 31% in the primary surgery group. Statistical analysis of those relations and possible prognostic factors is performed.

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P-73

Marginal resection can cure chemosensitive hepatoblastoma

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Classically resection of hepatoblastoma following anatomical planes (segmentectomy-lobectomy) is considered necessary for cure. However the margin of normal liver tissue which should be removed with the tumor is not well defined. There are indications from several tumours (Wilms tumour, congenital fibrosarcoma, osteosarcoma) that a small margin of resection may be sufficient when a good tumour response is obtained by pre-operative chemotherapy. Extensive liver resection for hepatoblastoma is not without morbidity and even 5% mortality in recent studies. We present a child, now 6 years from surgery who received chemotherapy and marginal resection for a central hepatoblastoma. The child presented at the age of 2 months with a large hepatic mass measuring 10x7x11 cm. The alpha-foetoprotein level (aFP) was 175 898 ng/ml. After 4 courses of chemotherapy (PLADO) cisplatin 80 mg/m2 per 24 hours infusion day 1 and doxorubicin 60 mg/m2 per 48 hrs infusion day 2 through day 3 the tumour measured 5x3 . 8 cm and the aFP level was 658 ng/ml. This can be considered a very good partial remission (VGPR). The tumour was centrally located between the ligamentum teres and the gallbladder (segment 4). Instead of doing an extended left hemihepatectomy a typical resection of the anterior part of segment 4 was performed vcery close to the border of the tumour. Both the right lobe and the lateral segments of the left lobe were preserved. The pathology of the resected specimen showed more differentiation than in the biopsy and that there was a small margin of compressed normal liver around the tumour. aFP levels continued to fall according the expected serum half life. The child is considered cured 6 years later. He is healthy, active and doing well at school.

In conclusion: this case illustrates that hepatoblastoma can be cured by a combination of chemotherapy and marginal resection. This approach should perhaps be considered in children with a VGPR to pre-operative chemotherapy who have central of multifocal tumours who would otherwise be subjected to transplant.

P-74

SEX-CORD STROMAL TUMORS OF THE OVARY IN CHILDREN: A REPORT OF 11 CASES.

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Sex-cord stromal tumors are rare neoplasms derived from the specialized blastemal mesenchyme that has the capacity to differentiate into either the stromal tissue (theca and Leydig cells) or the sex-cord tissue (granulosa and Sertoli cells). Because of their peculiar origin, theese tumors maintain the power of sexual ormonal production, giving rise to iso- and, less frequently, etero-sexual precocious pseudopuberty. Authors report their experience about 11 cases of sex-cord stromal tumors observed in the last 20 years. The age of patients varied from 11 months to 15 years, with a main age of 4 years. Nine girls were affected by juvenile granulosa-cell tumors, one by a granulosa-theca tumor and one by an androblastoma. All patients but the last one affected by the androblastoma who developed signs of virilization, manifested as first symptoms evidence of isosexual precocious pseudopuberty, with breast enlargment, vaginal bleeding, pubic hair and an increase of somatic growth. All children were treated with unilateral salpingo-oophorectomy and only in one case the Fallopian tube could be preserved. All of the patients with granulosa and granulosa-theca tumors had Stage 1a at surgery, while patient affected by androbastoma was found at Stage 1c for the presence of tumoral cells in the peritoneal fluid; nevertheless no radiotherapy or chemotherapy was given in any case. At the present all patients are alive and disease free with a follow-up ranging from 16 months to 20 years.

P-75

ONE-STAGE RECONSTRUCTION OF THE LOWER URINARY TRACT IN GENITOURINARY RHABDOMYOSARCOMA OF CHILDREN.

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Rhabdomyosarcoma (RMS) represent 4-8% af all malignant disease seen in children under the age of 15 years. Because of the direct relation between tumor site and patient age, genitourinary tract is affected in about 40% of infants, while this side is more less interested in the older children. In the last ten years radical changes have occurred in the treatment of rhabdomyosarcoma, thanks to a multidisciplinary approach which have dramatically improved the survival rate of these patients. Several studies have been performed to evaluate the role of chemotherapy, radiotherapy and surgery in the treatment of genitourinary RMS, stating that a radical operation rather than bladder sparing surgery, remains the successful form of therapy. Nevertheless, the goal of the surgeon should be to ensure the best quality of life in pediatric age. Colon-conduit is the more used temporary urinary diversion, but nowadays, thanks to the current surgical advances, radical surgery with one-stage lower urinary tract reconstruction should be considered the therapy of choice, since it may offer the same increased survival combined with an excellent quality of life. Authors report their experience in the last 3 children (2 male and one female, aging) affected by genitourinary RMS, in which a radical surgery was combined with bladder augmentation, bladder substitution and continent urinary diversion, respectively, with two umbilical Mitrofanoff free at a follow-up of conduit for clean intermittent catheterization. All children are alive and disease and show a normal upper urinary tract with complete urinary continence.

P-76

SUBTRACTIVE ENRICHED DIFFERENTIAL DISPLAY TO IDENTIFY MOLECULAR MARKERS IN MOUSE AND HUMAN LIVER TUMORIGENESIS

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Objective Identification of up- and down-regulated gene products (onco-/ tumor suppressor genes) responsible for the development of hepatocellular carcinoma (HCC). Test the expression of the identified gene products in mouse and human liver tissue.
Methods We compared cDNA fragments of tumor and normal liver tissue in the mdr2$^{-/-}$ HCC model. The subtractive-hybridization procedure was used to eliminate common gene products and to enrich the up- and down-regulated cDNAs. Differentially expressed fragments on a display gel were identified and used for complete cDNA isolation. cRNA probes were constructed for in situ hybridisation studies to screen expression in mouse and human liver tissue.
Results Over 20 up- and down-regulated cDNA fragments were so far characterized by nucleotide sequence analysis. Part of these cDNA fragments were known regeneration/ tumor-associated factors, whereas the remainder were novel, unknown gene products. Using selected, novel gene products from the display gel we could demonstrate differential expression of the products in mouse and human liver tissues by northern blot analysis (DNA probe) and by in situ hybridization localization studies (cRNA probe). We observed high cellular concentrations of glutamin synthetase (GS) mRNA in all cells of tumor nodules. Similar observations regarding GS were made in hepatoblastoma (HB). In larger tumor masses the localization was more dispersed in a subset of cells, both in human HB before chemotherapy

and in the mouse mdr2$^{-/-}$ HCC model. After chemotherapy the HB cells still expressed GS. A human fibrolamellar HCC before chemotherapy showed strings of isolated GS positive cells.
Conclusions The subtractive-hybridization procedure is a good method for the identification of molecular markers in livercarcinogenesis. Glutamine synthetase (GS) is often up-regulated in human and mouse liver neoplasms.

P-77

A REPORT OF THE JAPANESE STUDY GROUP FOR PEDIATRIC LIVER TUMOR(JPLT). ANALYSIS OF THE DEAD CASES.

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The regimen included more than 6 courses of chemotherapy (CDDP 80mg/m^2 i.v.24hr infusion and then THP-ADR 30mg/m^2 i.v.24hr infusion $\times$2). From June of 1991 to the end of 1993 58 patients with advanced liver tumor were registered to JPLT. Ten were dropped from the study and 3 patients were diagnosed as having hepatocellular carcinoma. Thirty two patients were analysed. Twenty eight patients survived more than two years. Four patients died of tumor with one stage III A, one stage III B and two stage IV patients. Pre-treatment AFP level did not correlate with prognosis. Pathological diagnosis of the dead cases consisted of 2 undifferentiated type, one macrotrabecular type and one unknown pathology. In 2 patients tumor was remained macroscopically and in 2 patients operation was not performed. Metastases were found in the lung and the liver. Most important factor was complete resection of the liver tumor. Aim of pre-operative chemotherapy is concluded as follows; to reduce unresectable liver tumor and prevention of pulmonary metastasis.

P-78

NEPRON SPARING SURGERY FOR UNILATERAL PRIMARY RENAL TUMOURS IN CHILDREN

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AIM. In adults with bilateral or unilateral renal cell carcinoma or oncocytoma (1,2) and in children with bilateral nephroblastoma (3), nephron sparing surgery (NSS) or nephrectomy have similar morbidity and mortality. Therefore, NSS may be a reasonable option even in selected children with unilateral renal tumour. To support this hypothesis, we report our most recent experience with NSS in children with unilateral neoplasm.
PATIENTS AND METHODS. Between January 1992 and February 1997, 17 children with primary renal tumour and a normal contralateral kidney were consecutively operated by a single surgeon. Possible candidates for NSS were evaluated according to certain criteria, including stage I disease , 50% of functioning kidney preservable, no unfavorable histology or microscopic disease on intraoperative frozen section biopsies from regional nodes, perirenal fat, surrouding renal parenchyma, and excised tumor. Pre-operative chemotherapy was given according to the SIOP study protocol.
RESULTS. Four elegible patients underwent NSS without hypotermia or vascular occlusion.Three of these had nephroblastoma and were treated with chemotherapy as for stage II disease.The fourth patient presented with oncocytoma and had no further treatment following NSS. All four patients are disease-free at 57, 56, 33 and 2 months of follow-up rispectively with a renal function almost completely restored. In another child with nephroblastoma, following a good response to pre-operative chemotherapy, NSS was considered not feasible due to firm adherences between the tumour and a thick pseudocapsule; ex situ enucleation after nephrectomy resulted in rupture of the tumour.
CONCLUSION. In children with unilateral primary renal tumours, exhaustive and cautious intraoperative evaluation plays a key role in selecting patients with localized disease and in establishing the feasibility of NSS.

1) Mall W et al. J Urol 150: 319-24, 1993
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P-79

RENAL ANGIOMYOLIPOMA. DESCRIPTION OF TWO CASES.

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We describe 2 cases of renal angiomiolipoma (R-AML) observed in our Institution during the last 3 years. ***Case 1.*** A 11 year old girl presented with an asymptomatic abdominal mass. Since the radiological investigations showed within the right kidney a huge solid-cystic mass, with patterns resembling a Wilms tumor, chemotherapy according to SIOP Study 9301 was started. No shrinkage of the mass was obtained after the first cycle, therefore surgery was carried out with diagnostic and therapeutical goals. A frozen examination demonstrated that the tumor was benign, however a nefrectomy was necessary in order to obtain a complete excision. The conclusive histological diagnosis was R-AML. The pt did not receive other treatment and he is disease free 30 months after diagnosis. ***Case 2.*** A 15 year old female was hospitalized because of an asymptomatic mass of the left flank. US and CT scan showed a solid renal tumor (8 cm in diameter). After a no conclusive echoguided FNAB, the surgical excision was planned: the frozen examination excluded a malignant tumor, but a left nephrectomy was performed because of the tumor's size. R-AML was the final histological result. At present the girl is disease free at 12 months from diagnosis.
R-AML is a benign tumor, rare in adults and much rarer in children. It consists of blood vessels, smooth muscle cells and mature adipose tissue, and *can mimic a Wilms tumor at imaging.* Two tipes may be found: 1) unilateral, large in size, generally asymptomatic; 2) bilateral, often associated with phacomatosis (especially tuberous sclerosis). A conservative surgery (partial nephrectomy) should be performed if feasible, without any other treatment.
It seems appropriate to emphasize to the pediatric oncologist and the pediatric surgeon the existence of this entity in order to adopt the right therapeutic approach.

P-80

Prenephrectomy chemotherapy on Wilms' tumor: epidemiological, clinical, and surgical features

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The administration of prenephrectomy chemotherapy in Wilms' tumor is still controversial. We evaluated epidemiological, clinical and surgical features in 602 children enrolled in successive trials by the Brazilian Wilms' Tumor Study Group with respect to the relative benefit of pre-operative vs. post-operative

chemotherapy. Of those receiving preoperative chemotherapy (N=150), 106 had inoperable tumors. These children were compared with 452 evaluable children who underwent primary nephrectomies. Children undergoing preoperative treatment tended to be older than those in the direct surgery group. The difference persisted when the comparison was restricted to children with localized tumors and no surgical rupture; mean ages were 41.8 and 30.1 mos for stage I disease (p=0.0527), 42.0 and 41.2 for stage II, 49.9 and 48.2 for stage III. This is consistent with a beneficial effect of preoperative chemotherapy via a decrease in tumor burden in addition to the expected reduction in risk of tumor rupture. Indication for preoperative therapy is highly dependent on the multidisciplinary team, which contributes to the prognostic heterogeneity of our preoperative group. Black children and children from institutions from the state of Bahia received more often preoperative chemotherapy. Among stage IV patients tumor rupture (local and diffuse) was significantly less frequent among those receiving preoperative chemotherapy. The hazard ratio (HR) for local tumor rupture for patients receiving preoperative chemotherapy vs. immediate surgery was 0.34 (95% confidence interval [95%]: 0.1-1.1). Expectedly, the mean tumor weight was substantially lower in the preoperative chemotherapy group than in the direct surgery group: 734.5 gms +- 318 vs. 361 gms +- 301. These results suggest that preoperative chemotherapy may be advantageous, particularly in patients populations presenting with advanced tumors.

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TREATMENT RESULTS OF THE SOFT TISSUE SARCOMA (STS) IN CHILDREN. A REPORT BY THE POLISH PAEDIATRIC SOLID TUMOR GROUP (PPSTG).

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In 1993 the PPSTG adopted the CWS-91 protocol for treatment of st.I-III of the STS and the SIOP-IV Intergroup Regimen for st.IV. The following study covers 102 pts aged up to 18 years , from who 62 had RMS and 40 non-RMS . The median follow-up was 23 mths.

Nine RMS pts (14.5 %) were in st. I-II, 40 (64.5 %) st. III and 13 (21 %) st. IV. The tumors were primarily localised : head-neck non-P.M. in 12 pts (19.4 %), head-neck P.M. in 15 (23.3 %), extremities in 11 (17.7 %), G.U. in 13 (20.9 %) and others in 11 (11.7 %) children. Lungs were the most common single organ with metastases (40 %). 3.2 % of all pts were classified to the prognostic group A, 16.1 % to group B and 59.7 % to C. 27.4 % had tumors volume >10 cm. Nine pts reached the CR after the primary surgery. The CR was achieved in 32 pts (80 %) in st. III and 8 (61.5 %) in st. IV. Two pts died prior to the CR assessment (infection, metabolic toxicity), 3 in CR (infections). Eleven children had relapses (22.4 %), 7 of them presenting st. III. Seven pts did not respond to the therapy. The EFS after 50 mths were 0.94 for st. I-II, 0.62 for st. III, 0.38 for st. IV, 0.94 for A-B risk groups and 0.61 for group C. There was no difference in EFS for RMS-E and RMS-A (0.7 vs. 0.74) in stage III. EFS for tumors <5 cm is 0.87, for tumors >10 cm - 0.38. EFS rates for CR, GR and PR+NR were respectively : 0.86, 0.64 and 0.37. The response to the 1st cycle and the initial tumor volume were significant prognostic factors.

Twenty non-RMS were chemosensitive (SS, extraosseous Ewing sa., PNET) - I group, 9 partially chemosensitive (MFH, vascular sa., leiomyosa.) - group II - and 11 not chemosensitive (fibrosa., liposa., malignant schwannoma) - group III. Twelve pts (30 %) presented st. I-II, 24 (60 %) st.III and 4 (10 %) st.IV. There were 15 % of tumors <3 cm and 25 % >10 cm. The CR was achieved in 34 pts (85 %) after the primary surgery (12), chemotherapy with radiation (11), secondary surgery (11). Eight children relapsed : 2 in the A (11.7 %), 3 in B (37.5 %) and 3 in C group (33.3 %). Ten children died - 5 non-responders and 5 due to relapse. The EFS and survival rates for all pts after 50 mths were 0.59 and 0.67. EFS in the non-metastatic pts was 0.8 in stage I-II and 0.58 in stage III. PNET survival rate was 0.88 and EFS 0.73. The EFS rate for groups I, II and III were 0.79, 0.5 and 0.56, with no prognosis difference between II and III.

P-82

RELAPSES IN THE FIRST POLISH WILMS' TUMOUR STUDY.

J.Godzinski, K.Sawicz, J.Czernik, A.Balcerska, M.Bagłaj, J.Bohosiewicz, P.Czauderna, P.Daszkiewicz, B.Dembowska, G.Dobaczewski, S.Kantorowicz, B.Kazanowska, K.Kątski, J.Kowalczyk, W.Madziara, D.Perek, M.Rapała, R.Rokicka, G.Skotnicka, B.Sopyło, C.Stoba, W.Woźniak, M.Wysocki, U.Radwańska. **For the Polish Wilms' Tumour Study.**

Since relapses (rel.) in pts treated for Wilms' tumour (WT) have become rare and general prognosis is excellent, management in case of treatment failure is of special interest. Aim. To evaluate rate, type and outcome of rel. in the I Polish WT Study. Patients. Records 206 pts have been collected (1.03.93-15.02.1997); age range - 0 to 14 years, stages - I in 27%, IIN- in 32%, IIN+ in 9%, III in 18%, IV in 9% and V in 5% of pts, histological variants of WT favourable - 11%, standard - 72%, unfavourable - 13% and non-WT - 4%. Relapses: 16 pts of 206 (follow up: x= 28, range 1 - 47 m) staged I in 4 cases, IIN- in 5, IIN+&III in 2 and IV in 5. Pathology: standard in 13 and unfavourable in 3. Types of rel.: metastatic - 7 pts, local - 2, regional lymphnodes - 1, combined (local +/- regional +/- metastatic) - 6. Treatment for rel.: In all but 2 (primary lung metastatectomy), ChT (VCR-Ifo-ActD-Epi) was the first treatment for rel. Favourable response to ChT allowed for successful local treatment in 9 pts (surgery +/- RTX). Outcome: 9 pts of 16 are still in II CR: 4 after metastatic rel. to lungs, 3 after combined rel, 1 after local rel. and 1 after isolated lymphnode rel. (follow up 5 - 32 m). Summary: 16 rel. of 206 pts is acceptable rate, however follow up is short. Stages I and IIN-, however most common among rel. pts. are also most frequent in all pts (59%). Majority were metastatic rel. alone or combined with lymphnode and/or local ones (13 pts of 16). Conclusion: Rel. in nephroblastoma is usually generalized disease and should be treated primarily with ChT and then operated on or irradiated on. Nine of 16 pts who relapsed are survivors. (KBN 4 S405 075 07)

P-83

PROGNOSTIC FACTORS IN CHILDHOOD MALIGNANT GLIOMAS

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Malignant gliomas in children are tumours with a very unfavourable prognosis. Little is known about prognostic factors in childhood, although histology, tumour localisation and extent of surgical resection are said to be important.

A retrospective study was performed of patients who were treated in our institute between 1985 and 1993. Pathology was reviewed. Patients with a supratentorial or spinal cord high grade glioma were included. Imaging studies were reviewed with measurement of tumour size and scoring of tumour characteristics. Tumour volume was estimated by multiplying maximum diameters in 3 dimensions.

The study population consisted of 50 patients (23 females and 27 males) with a median age of 10.4 years (range 0.6-20.8). Fourty six patients had a supratentorial tumour, invading central nuclei in 18 cases (39 %) and 4 a spinal cord tumour. The median estimated volume was 125 (range 8-340; n=22) on CT and 93 cm^3 (range 5-198; n=23) on MRI. In 11 patients in whom it was possible to compare CT and MRI, differences in tumour volume exceeded 30 cm^3 in 50 % of cases.

Surgery consisted of a biopsy in 15, partial resection in 13 and complete resection in 22 cases. Resection had been complete according to the surgeon in 3 out of 18 central tumours. There were 34 patients with a pure astrocytic tumour and 16 with a mixed oligo astrocytic tumour. Estimated overall 5 year survival was 39 %, with a relapse free survival of 26 %. Relapse free survival was 50 % if resection had been complete. Cox regression analysis with age, sex, histology, localisation, extent of surgical resection, start of radiotherapy and start of chemotherapy as covariates, demonstrated that a central site of the tumour (RR 2.62; $P<0.05$) and administration of radiotherapy (RR 0.29; $P<0.05$) were independent prognostic factors. Radiological signs, such as estimated tumour volume did not have a prognostic value. Thirteen patients were in complete remission after a median follow-up of 61 months (range 2.4-20.8). One had a central, completely resected, tumour. Five had a mixed tumour, 5 a grade IV and 3 a grade III astrocytoma.

It is concluded that survival is extremely rare in patients with central tumours. Relapse free survival is 50 % if resection has been complete. Administration of radiotherapy further decreases the relapse risk. Tumour volume and other radiological tumour characteristics do not seem to be related to prognosis.

P-84

TREATMENT (Tt) OF METASTATIC EXTRACRANIAL SECRETING GERM CELL TUMORS (mGCT)

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From January 1989 to December 1994, SFOP treated patients (pts) with mGCT by 6 cycles of Carboplatine (CarboP) based-chemotherapy (CT) followed by resection of tumor (T) residue. One cycle consisted of Vinblastin 3 mg/m² d1-d2, Bleomycine 15 mg/m² d1-d2, CarboP 400 mg/m² d3, Ifosfamide 1.8 g/m² d22-d26, Etoposide 100 mg/m² d22-d26. In case of incomplete biological remission or markers reelevation, Cisplatinum was introduced.
28 pts (18 males-10 females) were registered. Mean age was 29 months (m). 7 pts had sacrococcygeal (sc) primary T, 8 testis (t), 2 ovary (o), 1 mediastinal (med), 8 retroperitoneal (rp), 1 uterus (u). 20 T secreted αFP, 2 βHCG and 6 both markers. Initial histology was known for 14 pts on biopsy (10) or 1st surgical removal (3 t-1 o). Most often metastasis were pulmonary (18), hepatic (13) or adenopathy (11).
1 pt (o) is not evaluable because she was treated according to the non metastatic protocol (alive at 67 m). Among the 27 pts, 4 (1 t-2 rp-1 med) never achieved biological complete remission (CR) and died, 23 achieved biological CR: 18 after CarboP based-CT, 4 after adding Cisplatinum and 1 after adding Cisplatinum and high dose (HD) CT (Etoposide - Thiotépa). 20 pts out of the 23 had a complete resection of the residue (evolutive cells were found in 2 cases), 2 pts had incomplete resection and 1 no resection of the residue. These 3 partial remission relapsed: 2 died and 1 was salvaged by HDCT.
In total, 20 pts are in CR_1 with a median follow-up of 42 m (19 - 87) and 1 in CR_2 at 61 m. Overall survival is 75 % (+/- 18%) and EFS 78 % (+/- 16%) at 5 years.
Conclusion: CarboP based-CT including Ifosfamide and Etoposide is efficient in mGCT; surgery of T residue seems to improve prognosis. (Part of this work has been supported by the « Association pour la recherche contre le cancer »)

P-85

MULTIDISCIPLINARY APPROACH FOR SYNOVIAL SARCOMA (SS) IN CHILDREN

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SS is the third most frequent soft tissue sarcoma in children and it is preferably localized in the extremities. From January 1988 to December 1995 16 children with localized SS have been enrolled onto the ICS-RMS 88. Age: 17-196 months, 7 males. Tumor arose in the extremities (9 cases), head-neck (3), thorax (1), abdomen (1).
At diagnosis tumor was radically excised in 3 cases (IRS group I), in 13 residuals were left: microscopic in 4 (II), macroscopic in 9 (III). Group I-II pts. received 9xIVA (Ifosfamide 9 gr/m², Vincristine and Actinomycin 1.5 mg/m²) and radiotherapy (RT) 40 Gy. Group III pts received VAIA (Ifosfamide 10 g/m²; Actinomycin 1,5 mg/m² ; Adriamycin 80 mg/m²; Vincristine 1.5 mg/ m²) followed by 9xIVA and RT 40-70 Gy. After initial chemotherapy (CT) conservative surgery (S) was performed if feasible. In 8/9 evaluable group III pts CT response was: tumor stable in 4 cases, reduction>2/3 in 4. All pts achieved complete remission (CR): with S alone 5, S+RT 5, CT+RT 3, CT+RT+S 2, CT 1.
We observed 5 local relapse (1+metastasis). Fifteen pts are alive: 11 first CR, 1 third CR, 3 with disease. Five year progression free and overall survival were 67.4% and 91.7%. On univariate analysis group, invasiveness, size, site, nodes, CT response were not associated with prognosis.
Multidisciplinary approach provided good results, even if surgery was not possible. CT may be used to made feasible a conservative surgery or associated with RT when surgery is not feasible. Survival may be prolonged even after relapse.

P-86

TREATMENT OF NEUROBLASTOMA: EXPERIENCE OF THE İZMİR PEDIATRIC ONCOLOGY GROUP (IPOG) - 92 NBL STUDY

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Excellent survival of lower risk disease has been maintained with less therapy but survival for patients (pts) with high risk neuroblastoma (NB) has remained poor. The aim of this study was to assess the outcome of pts on IPOG-92 NBL protocol.
Patients and Methods: Between May 1992 and December 1996 38 eligible pts from four centers in İzmir were enrolled in the study. IPOG-92 NBL was originated from BFM-90 NB protocol with modifications in doses of drugs. It consisted of neoadjuvant chemotherapy (CT) (excluding the pts with stage I), followed by resection of the primary tumor. The induction CT included 2-5 cycles of alternating courses of VIDE/ PCVP (VCR, IFOS, DTIC, Epirubicine and CDDP, CTX, VP-16). The pts who achived CR or PR after induction CT received maintenance therapy consisting of 6 cycles of alternating two drug combinations (CTX, VCR and VP-16, L-PAM). Radiotherapy was administered to gross residues only.
Results: Fifty-eight percent of the patients were boys. Median age at diagnosis was 36 mo. The stages of the pts were as follows: Three stage (s)I, 2 sII, 2 s IVS, 13 sIII and 18 sIV. Four infants were younger than 12 months of age of whom 2 with stage IVS and 2 with advanced disease. Primary site was abdominal in 87 %. Initial excision and a second-look procedure were performed in 14 pts (37 %) and in 15 instances respectively. Pathology was consistent with NB in 32 pts (84 %). Median follow-up time was 13 mo. Sixteen pts (42%) were still alive of whom 11 were in CR, 2 in NR and 1 in PD. Ten pts have been lost to follow-up; among these 5 were in CR, 12 died after a median follow-up of 5 mo. Three pts had a recurrence in the primary site after 4 to 40 mo of diagnosis. The overall 2-yr survival (OS) and EFS rates for all pts were 68 % and 58 % respectively. Five pts with sI and sII were alive with a median follow up of 42 mo. The OS and EFS at 2-yr for pts with advanced disease were 60.7 % and 47.9 % respectively. Multivariate analysis showed that stage and primary site at diagnosis were the most important prognostic factors predicting the response to therapy.
Conclusion: To our knowledge, this is the first multicentric study from Turkey. These preliminary data indicate that overall outcome of localized NB is good, but no survival advantage is seen for advanced disease.

P-87

PRIMARY INTRACRANIAL GERM CELL TUMORS IN CHILDREN A REPORT OF NINE CASES

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Objectives: This study was carried out to evaluate the diagnosis, therapy, and survival of patients with primary intracranial germ cell tumors.
Materials: Nine patients with surgically confirmed primary intracranial germ cell tumors were treated and followed-up at Hacettepe University Department of Pediatric Oncology between 1974 and 1996.
Results: While one patient was admitted with a second recurrence of her disease, the others were admitted or referred primarily to our institution. In the same period, 359 germ cell tumor and 691 primary intracranial malignant tumor cases were diagnosed and treated at our institution. Thus,

germ cell tumors comprised 1.3 % of the primary intracranial malignant tumors, and 2.5 % of the germ cell tumors. There were 5 females and 4 males and the median age was 8 years (13 months to 12 years). On admission, the most common symptoms were diabetes insipidus (4/9) and vomiting (3/9). One patient also had Down's syndrome. Locations of the tumors were found to be suprasellar in four, in the IIIrd ventricle in two, and in the cerebral parenchyma, pineal and hypothalamic regions in the reminder. Three total resections, four partial resection and two biopsies were performed a tissue diagnosis was made at surgery. There were 4 germinomas, 3 malignant teratomas, and two mixed germ cell tumors. Only three patients could be treated with appropriate and adequate chemotherapy and radiotherapy. Three of nine patients died, one in the postsurgical period, one after the third surgical approach and the third died eleventh months after the diagnosis with progressive disease and three lost to follow-up. The remaining three patients including those with second recurrence and disseminated disease are alive without of disease.

Conclusions: Our experience in these patients, showed that appropriate and adequate chemotherapy is as effective as radiotherapy even in recurrence of the disease.

P-88

KAPOSI'S SARCOMA; RENAL TRANSPLANTED CHILDREN A REPORT OF THREE CASES

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Objectives: Only rare examples of Kaposi's sarcoma, unrelated to human immunodeficiency virus (HIV) in children receiving a renal transplant have been published. We describe the clinical features of three cases of pediatric Kaposi's sarcoma associated with allograft renal transplantation in HIV negative children.

Materials: We reviewed the medical records of three patients with Kaposi's sarcoma which developed after renal transplantation who were treated and followed-up in our institution since 1994.

Results and conclusions: At the time of diagnosis of Kaposi's sarcoma, the patients' ages were 16, 12, and 12 years. Median diagnosis time of Kaposi's sarcoma was approximately 6 months after the renal transplantation (4 to 18 months). All cases were female and they had been given immunosuppressive drugs because of renal transplantation. While two of them were admitted with reddish blue macules and plaques in the skin, the third had apparently infected granulomas in the perineal and perianal region and none of them had visceral involvement. The diagnosis was established by biopsy in all cases. Immunosuppressive drug doses had been reduced for treatment, but they needed to receive chemotherapy because of progression of their diseases. One patient received only systemic chemotherapy (cyclophosphamide+prednisolone+vincristine) one patient received systemic chemotherapy (vinblastine+ prednisolone), and radiotherapy followed by surgical resection and the third received different systemic chemotherapy (cyclophosphamide+ prednisolone, vinblastine+ prednisolon, methotrexate) and intralesional vinblastine. Median follow-up period is 26 months (6 to 27 months). All of them are alive and two are without disease at the present time.

P-89

SEQUENTIAL RAPID HIGH DOSE SINGLE AGENT CONSOLIDATION THERAPY FOR METASTATIC SARCOMA IN CHILDREN.

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Objective: This pilot study has been performed to assess the feasibility of sequential rapid high dose single agent therapy as consolidation treatment in children with primary metastatic or relapsed sarcoma.
Methods: The consolidation block consisting of A) cyclophosphamide 6 gm/m^2, B) etoposide 2.4gm/m^2, C) cyclophosphamide 6 gm/m^2 and D) carboplatin AUC 24 (followed by stem cell/ABMT rescue) was scheduled to be given at 14 day intervals with growth factor support.
Results: During the period from December 1995 to February 1997, 13 children (6M, 7F) aged 5.4 - 18.2 yrs have completed the consolidation block with full data. Diagnoses include RMS (3 embryonal, 5 alveolar), Ewing's sarcoma (2), PNET (1), synovial sarcoma (1) and undifferentiated sarcoma (1); 9 were treated at 1st presentation (following induction therapy as given in MMT Stage IV 89) and 4 were treated at relapse. Twelve patients had PBSC collections, taken prior to (9) or after (3) course A; the remaining patient had an ABMT. The median time intervals between courses A, B, C, D were 16, 16 and 21 days respectivelv. Following carboplatin, median times to neutrophil (>1x10^9/l) and platelet (>50x10^9/l) recovery were 15 and 45 days respectively. In addition to expected haematological and infectious toxicity, important renal (1 Grade 2, 1 Grade 3, 5 tubulopathy) and gastrointestinal (1 VOD, 2 pneumatosis coli) toxicities were encountered following carboplatin. There were no toxic deaths.
Conclusions: Rapid high dose single agent therapy is a feasible therapeutic option. In view of the toxicity encountered following the carboplatin, dosage has now been modified to AUC 20. The efficacy of the modified schedule incorporated into a treatment protocol for metastatic sarcoma should be further evaluated.

P-90

Long Term Survival of Childhood Hemophagocytic Syndrome

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This study was undertaken to investigate the long term survival of childhood hemophagocytic syndrome (HS) treated with immunoglobulin (IVIG) and/or VP-16-containing regimens. **Material and Methods:** Twenty-seven children diagnosed as HS from two hospitals between 1990 -1996 were studied. Fifteen were boys and 12 were girls with age ranging from 9 d/o to 17 y/o. Their treatment mainly consisted of IVIG (2gm/kg) and/or VP-16-containing regimens. **Results:** The significant clinical manifestations included prolonged fever, neutropenia, anemia, thrombocytopenia, hepatomegaly, splenomegaly, increased GOT and/or GPT, hypertriglyceridemia, and marked elevation of LDH. Seventeen out of 27 children were alive at the end of study. Six patients followed a fulminant fatal course and 9 cases experienced a relapsing course. Two cases turned out to be peripheral T-cell lymphoma and one of them was fatal. Twelve patients are still disease-free, with a mean follow-up of 43 months (5-80 months) since treatment start. The 3 years overall survival rate and disease free survival rate are 53% and 68%, respectively. **Conclusion:** Immunomodulation therapy with IVIG and/or VP-16-containing regimens are effective for most cases of childhood HS. But, a substantial subgroup of childhood HS experienced a relapsing and even progressive fatal neoplastic course. More intensive chemotherapy should be applied to such patients than those we used currently.

P-91

TREATMENT RESULTS OF 101 PATIENTS WITH non-RMS SOFT TISSUE SARCOMAS. 31 YEARS OF EXPERIENCE FROM ONE INSTITUTION

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The analysis of treatment results in 101 children with non-RMS soft tissue sarcomas (nRSTS) according to treatment strategies changing in time and main clinical characteristics as possible prognostic factors was performed.

During 1962-1993 (31 years) 101 patients (pts) with nRSTS were treated, 53 boys and 48 girls aged from 1mos to 17yrs 10mos (median age -7yrs 1mos). 51 pts (50,4%) are alive with a follow up from 3 yrs to 31yrs.

The changing treatment strategy had a great impact on the survival, especially in advanced disease. In the first period when surgery (often mutilating) and radiotherapy(RTX) were prevalent -the general survival in the III group was 19,2%, in the second one with systemic (induction and adiuvant) chemotherapy (CHT) -CYVADIC, IRS-III protocol, delayed surgery and RTX -the survival was 48,2%.

The following factors influenced prognosis: histology (the best survival 77,7% in fibrosarcoma, the poorest 0% survival in liposarcoma), clinical advancement according to IRS-CWS91 classification (I group - 100%, II group - 67,8%, III - 34,5%, IV - 0), tumor location (68 % in peripheral parts of extremities, 33,3% inabdominal wall), tumor size (85% in tumors < 5 cm of diameter vs 37,8% in tumors >5cm), surrounding tissue infiltration (T1-80,5% vs T2-33,8%) and lymph nodes involvement (No-77,7% vs N1 - 32,1%).

The treatment failures were caused by progression during treatment in 36%, local relapses in 27,6%, local and distant metastases in 12,7% and distant metastases in 23,4%.

Our results dictate the necessity to intensify induction CHT as well as to perform radical local therapy (surgery, RTX) to ensure local tumor control.

P-92

THE ROLE OF CHEMOTHERAPY IN THE TREATMENT OF RETINOBLASTOMA.

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The efficacy of adjuvant chemotherapy /CHT/ in extraocular retinoblastoma /RB/ has been established.
The introduction of neoadjuvant CHT in the treatment of patients/pts/ with intra--ocular RB aims to cure more children while at the same time preserving bilateral vision by reducing retinic scaring after laser therapy in low stage lesions and by eliminating enucleation and external beam irradiation in advanced intraocular disease.
Since 1994 in our Department we have introduced neoadjuvant CHT consisting of carboplatin,etoposide and vincristine in intraocular unilateral and bilateral tumors followed by local treatment which depended on the tumor's response and included criotherapy ,laser therapy,plaques,external beam irradiation and enucleation.
Seventeen pts were treated, 8 boys and 9 girls,aged from 1 to 70 months/mos/ There were 13 pts with bilateral/ one of them with massive extraocular and central nervous system spread/ and 4 with unilateral disease.
All patients are alive with a follow-up ranging from 1 to 35 mos /median -9mos/.
Secondary enucleation was performed in 3 pts showing no viable tumor cells in one pt, no extraretinal extension in the second and microscopic residual at the optic nerve cut in the third.
Five pts underwent irradiation /external or plaques/. Shrinkage of the tumor permited to perform crio or laser therapy in 4 pts without any further local management. One pt didn't require any local treatment at all.
The rest of the pts are currently on CHT.
CHT consisting of carboplatin, etoposide and vincristine is highly effective in reducing mass of intraocular RB and in permiting less agressive local treatment. Further evaluation of this method is needed.
We propose this approach in all pts diagnosed with hereditary and sporadic RB.

P-93

FETAL RHABDOMYOMATOUS NEPHROBLASTOMA: A TUMOR OF GOOD PROGNOSIS BUT RESISTANT TO CHEMOTHERAPY.

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Introduction: Fetal rhabdomyomatous nephroblastoma (FRN) is a rare variant of Wilms' tumor. The tumor chiefly consist of fetal striated muscle with particularly distinct striations and central nuclei.
Aim: To determine the effect of (preoperative) chemotherapy (CT) in the treatment of this subtype of nephroblastoma.
Patients and methods: By 1 Nov. 91, SIOP 9 had registered 852 patients (pat.) from 55 centers. We report 13 children diagnosed of FRN between 88-92 with a median age of 4 years (y) and 2 months(m) (range 1 m- 8y 6m). There were 7 boys and 6 girls. Nine patients were classified as stage I, 2 as stage II, 1 as stage III and 1 as stage V. Twelve patients received preoperative CT with Actinomycin-D and Vincristine for 2 weeks (1 pat.), 4 weeks (5 pat.) and 8 weeks (6 pat.) respectively. One patient was treated by two different kinds of preoperative CT. He was first misdiagnosed as neuroblastoma and finally diagnosed as a FRN after surgery.
Results: The volume of the tumor (determined by ultrasonography) did not decrease after 2 weeks of preoperative CT (1 pat.). After 4 and 8 weeks of CT the mean tumor regression was respectively 1.8% (8/12 pat) and 35% (6/12pat). Eleven patients are alive and free of disease for a mean follow up of 4 y. One patient was lost to follow up after 3 m due to a war and one patient died almost 2 years after nephrectomy but not due to his tumor.
Conclusion: This variant of Wilms' tumor is a bad responder to preoperative CT and is associated with a generally favorable outcome in most of all unilateral cases when treated by surgery.

P-94

LOCALIZED EWING'S SARCOMA OF BONE: RESULTS OF THE ITALIAN COOPERATIVE STUDY.

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The main goal of this study is to improve the overall survival (SUR) and the event free survival (EFS) of patients (pts) with localized Ewing's sarcoma of bone. The patients are treated with multimodal protocol caracterized by: a) high dose chemotherapy(CT) and hyperfractionated and accelerated radiation therapy(RT); b) addition of Ifosfamide(IFO) and Etoposide(VP-16) to standard chemotherapy with: Vincristine(VCR), Actinomycin-D(Act-D), Adriamycin(ADR), Cyclophosphamide(CPM). Other objectives are to evaluate the prognostic significance of age at diagnosis (≤ 14 yr vs > 14 yr), tumor site (pelvis vs extremities vs other sites), tumor volume (< 100 ml vs > 100 ml) and chemotherapy-induced tumor necrosis (grade I evidence of microscopic foci + grade II evidence of macroscopic foci vs grade III total necrosis).
MATHERIALS AND METHODS. Protocol outline. Pts ≤ 30 yr of age with newly diagnosed non metastatic Ewing's sarcoma or PNET of bone are elegible. Induction CT 3 courses, every 3 wk: two courses of VAdrC (VCR + ADR + CPM) alternating with one course of VAI (VCR + Act-D + IFO). Local treatment: RT is performed only if radical tumor resection is not feasible or incomplete tumor resection occurs; a total dose of 6080 cGy in hyperfractionated and accelerated modality is given. Maintenance CT: Phase 1: 5 courses, every 3 wk, VAdrC alternating with VAI. Phase 2: 5 courses, every 3 wk, VP-16 + IFO alternating with VCR + Act-D + CPM.
Patients. Between nov.'91 and Jan.'97 138 pts were enrolled in this study. 134 pts evaluable (4 too early): 87 males/ 47 females; 67 pts were ≤ 14 yr at diagnosis. Primary sites were: extremities in 81 pts; pelvis in 25, other sites in 28. Local treatment. 75 pts (56%) had surgery alone; 38 (28.4%) had RT as local treatment; 21 (15.6%) had surgery and RT. Regarding pts ≤ 14 yr, 46 (68.6%) pts had surgery alone; 12 (18%) had RT as local treatment; 9 (13.4%) had surgery and RT.
RESULTS. As of Jan.'97, with a median follow-up of 31 months, 111/134 pts remained event-free. 1 pt presented local progression of disease and successively died. 2 pts died on therapy because of toxicities: 1 pt because of typhlitis after local treatment with RT on pelvis area; the other pt because of sepsis. 20 pts (7 ≤ 14 yr) relapsed: 14 pts (5 died) with metastatic disease, 1 pt died with local recurrence(temporal bone) and 5 pts (4 died) with local recurrence plus metastases. The 4 yrs EFS rate is 78% (SE 4.3). The 4 yrs SUR is 84.8% (SE 3.7).The 4 yrs EFS rates compared for: treatment = surgery (79.3%) vs RT (70.4%) vs surgery+RT (89.5%); tumor site = pelvis (72%) vs extremities (82.8%) other sites (68.7%); age at diagnosis = ≤ 14 yr (84.8%) vs >14 yr (70.8%); tumor volume(70/134 pts) = < 100 ml (82.2%) vs > 100 ml (60.9%, p= 0.04); chemotherapy-induced necrosis (75/134 pts) = grade III (100%) vs grade I /II (63.9%, p=0.002).
CONCLUSIONS. The EFS and SUR rates can be considered satisfactory. Of more concern is the restricted indication to RT, especially in paediatric pts. The comparative study of the EFS by age, treatment and by tumor site doesn't show statistical significance; on the other hand the EFS compared by tumor volume show better results for patients with a tumor volume at diagnosis < 100 ml. The prognostic value of chemotherapy-induced necrosis is also confirmed.
(Supported by the National Research Council, Project n.. 9500435 PF 39)

P-95

GOOD RESPONSE OF RELAPSED OR REFRACTORY WILMS' TUMOR TO AN INTENSIVE COMBINED THERAPY (PROTOCOL CHLA-91LA2).

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The treatment of Wilms' tumor after using a first-line treatment is a challenging situation for the pediatric oncologist. Several different therapy strategies have failed to assure a long-term disease-free survival.

Since 1993, thirteen patients (6 boys and 7 girls) with a median age of 47 (range : 11-122) months at diagnosis of the primary tumor, were treated at the Hospital de Pediatría Garrahan, Argentina, after relapse (8), refractory disease (2), failure of another second-line therapy after relapse (2) and metachronic tumor (1). All patients had been treated previously according to a modified National Wilms' Tumor Study-4. At diagnosis, 2 patients had been stage I, 4 patients : stage II, 1 patient : stage III, 2 patients : stage IV, and 4 patients : stage V. Two children of this last group had had also metastatic disease at onset. After relapse, therapy was according to a protocol for the treatment of WT with unfavorable histology or recurrent disease from the Children Hospital Los Angeles (CHLA-91LA2) and consisted of 4 courses of carboplatin (560 mg/m² - Day 0), etoposide (100 mg/m² - Days 0, 1, 2), ifosfamide (1800 mg/ m² - Days 21-25), and Doxorubicin (30 mg/m² - Days 21 and 22). After 2 courses of chemotherapy, patients were to receive radiotherapy, but for different reasons, only 6 did. Seven patients underwent some kind of surgery. Complete remission was achieved in 10 cases and 3 developed progressive disease. Two patients relapsed at 10 and 43 months after second remission, and subsequently died. With a median follow-up of 28 (range : 0-45) months, at 40 months the event-free survival and overall survival estimates (standard error) are 0.68 (0.13) and 0.75 (0.12), respectively.

We conclude that this therapeutic regimen for recurrent or refractory Wilms' tumor is highly effective. These results must be evaluated with a longer follow-up. Further studies, with larger numbers of children accrual, are warranted.

P-96

MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS IN 436 CHILDREN WITH STAGE IV NEUROBLASTOMA: A CHILDREN'S CANCER GROUP (CCG) STUDY.

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The outlook for stage IV neuroblastoma has remained poor, despite intensification of therapy. We compared the survival according to multiple clinical and biological risk factors for 436 children with stage IV neuroblastoma >1 year at diagnosis who were treated on CCG-3891 with intensive multimodality therapy. The overall EFS for the entire group including all randomizations at 3 years is 23%. Univariate and multivariate analyses were performed for age, bone marrow metastases by standard histology and immunocytology (BMI), bone metastases, surgical resection at diagnosis *MYCN*, ferritin, and Shimada classification. In univariate analysis, only *MYCN*, serum ferritin, and BMI at 12 weeks were significant, all with P<0.003. In bivariate analysis, patients age 1-2 yr. who had tumors with non-amplified *MYCN* had a significantly higher 3-yr EFS (74%) than the group of patients >2 yr. with non-amplified *MYCN* (EFS=24%) and the most unfavorable group, those with *MYCN* amplification regardless of age (EFS=15%). A similar pattern was seen with bivariate analysis of ferritin and age, in that ferritin appeared to have greater prognostic power in the 1-2 yr. age group compared to those over 2, although significant in both. Bivariate analysis of ferritin with *MYCN* showed that each were independent prognostic factors. Bivariate analysis of BMI at 12 weeks with *MYCN*, age, ferritin showed that BMI>100 tumor cells/10^5 nucleated cells remained an independent unfavorable prognostic factor. Multivariate Cox regression showed that *MYCN*, ferritin, and age were all significant (P<0.04) and independent, with an especially strong effect of age in patients with single copy *MYCN* tumors (P=0.011). Thus, even within stage IV neuroblastoma >1 year at diagnosis, *MYCN* amplification (EFS 16%), elevated serum ferritin (EFS 17%), and poor response to induction therapy by BMI (EFS 7%) all identify an ultra-high risk group who should be selected early for novel therapies.

P-97

INACTIVITY OF HIGH DOSE CYCLOFOSPHAMIDE IN HIGH GRADE ASTROCYTOMAS IN CHILDREN.

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The prognosis for childhood high grade glioma treated with surgery and radiation therapy is poor. Despite clinical trials have attempted to validate the role of chemotherapy in childhood high grade gliomas, the real efficacy of specific antineoplastic agents remains undetermined. We report the results of a phase II study of high dose cyclofosphamide in childhood high grade gliomas. From January 1994 to December 1996 10 children (3-15 years of age, median 8 years) with measurable high grade glioma on MRI have been treated. Four children had histologically proved glioblastoma multiforme and 4 children had anaplastic astrocytoma. Two children had diffuse intrinsic brainstem glioma. One patient had glioblastoma multiforme as a second tumor. Seven children have been treated at diagnosis and 3 children following radiation treatment. Chemotherapy was administered in two consecutive days at dose of 4 g/m² in 7 patients, at 3 g/m² in 2 patients and at 6 g/m² in 1 patient. Four weeks after chemotherapy clinical response was evaluated by MRI. No response was observed. In all patients tumor progression was documented and treatment was discontinued. Hematologic toxicity was severe. Grade 4 neutropenia has occurred in all patients; grade 3-4 trombocytopenia and grade 3-4 anemia requiring transfusion of blood products also has occurred in patients receiving cyclofosphamide at dose of 4-6 g/m². There have been no toxic deaths. Although escalating dose of chemotherapy have been utilized to overcome the intrinsic chemoresistance of high grade glioma, the lack of response in our sampling size indicates a very low probability of effectiveness of the treatment tested (error β = 10%) (Gehan J Clin Dis 1961, 13:346) and do not support the use of high dose cyclofosphamide previously reported in childhood high grade gliomas.

P-98

Carboplatin, Etoposide, and Vincristine Chemotherapy and Local Treatment for Intraocular Retinoblastoma

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Objective: In an effort to avoid enucleation (enuc) and external beam irradiation (EBRT) in children with retinoblastoma (RB), we have investigated the efficacy of chemotherapy and local measures in the treatment of newly diagnosed RB.
Methods: Of 156 patients with newly diagnosed RB seen over a 28 month period, 32 patients with 52 involved eyes had as the only treatment option enuc or EBRT. In an effort to avoid these modalities, patients were treated with chemotherapy consisted of carboplatin 18.6 mg/kg, etoposide 5 mg/kg daily for 2 days, and vincristine 0.05 mg/kg (CEV) for 2 to 6 cycles. All patients were treated with local measures to the smallest possible area consisting of cryotherapy, laser photocoagualtion, plaque irradiation, and thermotherapy.

Results: Of the 52 eyes treated on study 22 (43%) were controlled without the use of EBRT or enuc.

		Final eye treatment			
R-E Group	#eyes	enucleation	EBRT	Local	none
1	1	0	0	1	0
2	5	0	2	3	0
3	9	0	0	9	0
4	1	0	1	0	0
5	36	8	19	8	1
3	52	8	22	21	1

The major limitation to this approach is the presence or development of vitreous or subretinal seeds. Of the 8 patients requiring enucleation, 6 had vitreous seeds, 1 had subretinal seeds and 1 vitreous hemorrhage.
Conclusions: Combination chemotherapy with CEV and local measures is effective for control of intraocular RB. Had conventional treatment been used, 30 eyes would have been treated with enuc, and 22 with EBRT. With the use of CEV and local measures, only 8 eyes were enucleated and 22 were salvaged without use of EBRT or enuc. Higher stage, and the presence or development of vitreous seeds, predicted a poor response to this approach.

P-99

SYNOVIAL SARCOMA IN CHILDREN AND ADOLESCENTS: 30 YEARS OF EXPERIENCE WITH MULTIMODAL THERAPY.

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Charts of 39 children and adolescents were retrospectively reviewed; 22 were male, 17 were female. Median age was 11.4 years (range 5.7 to 16.9). Twenty-four were Caucasian, 10 were Hispanic, 4 were African American and 1 was Oriental. Median tumor diameter was 5.5 cm (range 1 to 17 cm). According to the IRS clinical grouping system, 24 had Group I, 10 had Group II, 2 had Group III, and 3 had Group IV disease. Primary sites were lower extremity 21; upper extremity 9; trunk 5; and head and neck 4. Histologically 20 were biphasic, 18 were monophasic and 1 was not specified. The treatment varied according to the time of diagnosis and tumor size/location, as follows: surgery (S) and chemotherapy (C) (pre or postoperatively) 15; S, radiotherapy (R) and C 14; S and R 6; S only 3, and C only 1. With a median follow-up of 6.8 years, the survival rate is 74% (29/39); Group I 22/24; Group II 7/10; Groups III + IV 0/5. One patient died from telangiectatic osteosarcoma secondary to radiotherapy. All of the patients who were Group III or IV died in spite of different modes of treatment. Of the 9 who died from synovial sarcoma, 8 were more than 10 years old and had maximum tumor diameter of >5 cm at the time of diagnosis; 6 had biphasic tumors and 3, monophasic. Survival by histologic type was 83% (15/18) with monophasic tumors and 65% (13/20) with biphasic tumors ($P > 0.05$). Of the 10 Group II patients with microresidual disease after S, 3 were treated with C successfully; of the other 7 who received R (7) + C (4), 4 are alive and disease-free. Postoperative C and R seemed to be effective for patients with microscopic disease, although the number of patients in this group was small. Gross total removal of the primary tumor was necessary for long-term survival. Proof of efficacy of non-surgical treatment, especially C, will require a randomized comparison with larger numbers of patients.
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P-100

PRELIMINARY TREATMENT RESULTS IN CHILDREN AND ADOLESCENTS WITH LOW RISK NON-TESTICULAR MALIGNANT GERM CELL TUMORS (MNT GCTS) (GPOH MAKEI 95 STUDY)

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Background: A postoperative watch and wait- (ww) strategy has proven to be safe in boys with testicular mGCTs [Haas et al., MPO 23: 400-405 (1994)]. Therefore for children with completely resected low risk non-testicular mGCTs a ww-strategy or a reduced chemotherapy was stratified in the GPOH MAKEI 95 study.
Patients and methods: From 10/93 to 2/97 patients (pts) with low risk mNT GCTs up to TNM stage T2 N_0M_0 were registered. Treatment consisted in complete resection alone (ovary T1a/b, extragonadal T1a) or resection followed by PE-chemotherapy (cisplatin 20 mg/m² day 1-5, VP16 100 mg/m² day 1-3, 2 courses for ovarian and 3 courses for extragonadal primaries). Relapse was treated according to high risk mGCTs.
Results: 13 pts were eligible. The ovary was the primary site in 11 cases, 2 cases presented as coccygeal primaries. Histology was YST (n=8) and dysgerminoma (n=5). Median observation time was 9 months (range 1-33). 2 pts received adjuvant PE, 2 pts non-protocol chemotherapy, 8 pts ww. Only 2 pts relapsed (both YST after 3 and 7 months) following resection and ww. Both relapses were diagnosed by raised AFP and treated with PEI (PE + ifosfamide 1.500 mg/m² day 1-5), both are in 2nd remission.
Conclusions: For low risk non-testicular mGCTs a reduced therapy including a ww-strategy is possible. However, a close follow-up is mandatory. This treatment policy may avoid adjuvant chemotherapy in about 2/3 of the defined low risk patients.
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P-101

ADJUVANT AND NEO-ADJUVANT SANDWICH CHEMORADIOTHERAPY FOR MEDULLOBLASTOMA - LONG-TERM SINGLE CENTER RESULTS

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Purpose: To test the efficacy of a sandwich polychemoradiotherapy as an adjuvant or neo-adjuvant regimen in non metastasized medulloblastomas.
Methods: Between Sep. 1986 and Jan. 1996 21 patients (pts.) (17 male, median age 8.3 years, 1.1-16.4 years) entered a single center study. 2 cycles of VEP (vincristine 1.5mg/m² day 1 and 8, dibromodulcitol 300 mg/m² day 1, 8 and 15, procarbazine 100mg/m² day 1-15) followed by 2 methotrexate infusions (MTX, 5g/m² + leucovorin rescue + MTX i.t.) after each VEP in 2 subsequent weeks were given in the neo-adjuvant regimen (only 1 VEP + MTX in the adjuvant regimen). In addition craniospinal irradiation was administered (36 or 24 Gy) with a boost to the posterior fossa (55 Gy). For consolidation 2 infusions of cisplatinum (CDDP 90 mg/m²) and 2 further VEP cycles were given, alternately. Since 1992 dibromoducitol was replaced by ifosfamide (3g/ m²,day 1 and 2, VIP). Pts.<2 years got maintenance chemotherapy, 3xVIP, 2x CDDP, 2x MTX instead of irradiation.
Results: The probability of event-free survival (EFS) is 0,7 (SE 0,1) at a median observation time of 6,2 years. Pts. with total tumor resection fared better. Out of 15 pts. analyzed for susceptibility to preradiation chemotherapy 12 (80%) responded. In pts. with nonresponse and partial response, respectively events are more frequent (p=0,009). One pt. (diagnosed at age <2 years) remained in remission over the last 6 years without any irradiation. Only 5 pts. were treated according to a neo-adjuvant regimen. 3 were nonresponders, 1 pt. showed a total and a 2nd pt. a partial regression after chemotherapy and both stayed in complete remission until now. EFS is not different no matter whether dibromodulcitol or ifosfamide is given and the whole chemotherapy schedule is applicated or not.
Conclusions: Sandwich polychemoradiotherapy in medulloblastoma is reasonable because it results in an early reduction of the tumor in most pts. The neo-adjuvant regimen has to be tested in future protocols because tumor reduction after initial chemotherapy leads to better conditions for tumor resection and thus may improve the overall outcome in medulloblastomas.

P-102

OSTEOSARCOMA (OS) AS A SECOND MALIGNANCY
Experience of the Cooperative Osteosarcoma Study Group (COSS)

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Objectives: To describe patient and tumor characteristics of OS occurring as a second malignant neoplasm and to evaluate the outcome of affected patients when treated according to modern multidisciplinary protocols.
Methods: All patients registered at the COSS-study-center between 1/80 and 6/96 whose OS arose as a second malignant disease were evaluated.
Results: 31 cases of secondary OS occurring a median of 87 months (range: 29-216) after diagnosis of a first cancer were registered. The first malignancies had been retinoblastoma (n=10), rhabdomyosarcoma (n=5), Ewing-tumor (n=4), fibrosarcoma (n=1), lymphoma (n=5), gynecologic tumors (n=3), gastric cancer (n=1), histiocytosis X (n=1) and medulloblastoma (n=1). Treatment had included radiotherapy in 25, chemotherapy in 25 and surgery in 20 cases, respectively.
13 secondary OS were situated in the trunk or skull, 18 in an extremity. 16/31 OS were located within a former radiation field. 3/31 patients presented with primary metastases of OS (2 skip, 1 lung). Local control was achieved in 21 patients. All 31 patients received chemotherapy, only 9/31 a complete COSS-regimen. After 7,5 years median follow-up, actuarial survival was 46% for all 31 patients (63% for 21 patients with local tumor control; no patient without local control survived past 3 years).
Conclusion: Provided local control is achieved and chemotherapy applied, the prognosis of secondary OS can be similar to that of primary OS.

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P-103

OUTCOME OF SURGERY ALONE OR SURGERY PLUS CISPLATIN/ ETOPOSIDE/BLEOMYCIN (PEB) FOR LOCALIZED GONADAL MALIGNANT GERM CELL TUMORS (MGCT) IN CHILDREN: A PEDIATRIC INTERGROUP REPORT (CCG8891 / POG9048).

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OBJECTIVE: Chemotherapy following surgical resection has been standard management for localized gonadal MGCT in children. Some reports suggest surgery alone may be adequate for infants with St I testis MGCT. To better define the roles of surgery and chemotherapy in curative treatment, this trial evaluated 137 patients with St I or II MGCT of testis (Te) or ovary (Ov).
METHODS: Eligibility required histologic confirmation of yolk sac (YS), embryonal (E), and/or choriocarcinoma (C); age<10y for St I and II Te, age≤21y for St I and II Ov; St II malignant recurrences from St I Te without prior chemotherapy. POG/CCG staging system: St I - limited to Te/Ov, appropriate post-resection fall in serum tumor markers; St II - microscopic residual or positive lymph node(s)≤2cm. Patients with pure mature (T) or immature teratomas (IT) and pure germinomas were excluded. Treatment was high inguinal orchiectomy for St I Te; surgery + PEB x 4 cycles (P: 20mg/M2/d + E: 100mg/M2/d x 5d plus B: 15mg/M2 on d 1) at 21d intervals for St I Te recurrences, St II Te, St I and II Ov. Histologies - Te(N=79): YS(73), T+YS(4), IT+YS(1), E(1); Ov(N=58): YS(14), T+YS(5), IT+YS(24), mixed (14), C (1).
RESULTS:

N	St/Site	Treatment	Events	2yEFS(SE)	2ySurvival(SE)
65	St I Te	Surgery	11	82%(6%)	100%
19*	St II Te	Surgery+PEB	0	100%	100%
42	St I Ov	Surgery+PEB	2	95%(4%)	95%(4%)
16	St II Ov	Surgery+PEB	2	94%(7%)	100%**

*-includes 5 failures from St I Te **-1 alive with progressive disease

All (11) St I Te recurrences were salvaged, 5 with PEB as St II; 2 Ov progressed despite PEB. Other Ov events included 2 secondary AML (1 alive post-BMT; 1 death). 134/137 survive free of MGCT at median followup of 2.5y. **CONCLUSIONS:** Surgery alone followed by surveillance is the therapy of choice for St I Te. Surgery+PEBx4 cycles is effective, well tolerated treatment for St II Te, St I& II Ov, and recurrent St I Te MGCT in children.

P-104

ORAL CHEMOTHERAPY FOR CHILDREN WITH GLIOBLASTOMA AND BRAIN STEM TUMORS

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A clinical trial was initiated to evaluate the role of oral chemotherapy in malignant glioma. Patients were treated postoperatively with 54 Gy conventional fractionated radiotherapy. Chemotherapy (Etoposid 25 mg/m2/d combined with trofosfamid 100 mg/m2/d for one year) started concurrently.

From July 1995 to February 1997 31 children (14 boys, 16 girl, 5 months - 19 years old) have been enrolled. 13 had supratentorial GBM. One of them had NF-I, 3 secondary GBM after acute lymphoblastic leukemia. 18 patients had brain stem tumors. 13 of them were enrolled based on the typical MR-scan morphology of a diffuse pons glioma, five of them were biopsied (1 AA, 4 GBM). 5 brain stem glioma outside the pons were GBM.

Observed side effects included mild leucopenia, mild thrombocytopenia and microhematuria. No treatment-discontinuation became necessary. 21/31 patients are alive (supratentorial 9/13; brain stem 12/18) after an average follow up of 282 days. 14/31 are alive without evolutive tumor (supratentorial 7/13, brain stem 7/18). Progression occurred after an average time of 184 days (supratentorial 193; brain stem 179). Probability of 1-year over all survival (progression free survival) was 58% (34%) in all, 63% (47%) in supratentorial tumors and 54% (27%) in brain stem tumors.

In summary, this protocol is not toxic and the survival does not appear to be different from high dose protocols.

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P-105

CNS Metastasis in Wilms' Tumour: a review of three consecutive United Kingdom Trials

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Data from three consecutive United Kingdom Children's Cancer Study Group trials, UKW 1, 2 and 3, are reviewed, focusing on intracranial metastasis. Six children out of 1269 registered children with Wilms' tumour developed CNS metastases between 2 and 27 months after initial diagnosis. One patient was initially treated according to UKW-1 , three were treated according to UKW-2 and two according to UKW-3. All patients were initially reported to have favourable histological features. Initial stages (patients numbers) were I (1), II (1), III (1), IV (2) and IV bilateral (1). One child with markedly reduced tolerance to chemo- and radiotherapy developed a single brain metastasis in the absence of pulmonary disease. Five patients had

metastases involving one or both lungs (median 4 deposits), including two with massive pulmonary disease. Surgical resection of the CNS deposit was performed in 4 patients and was complete in one. Post-operative radiotherapy was administered to 4 patients. Three patients are survivors with a mean follow up of 61 months from relapse. All received chemotherapy and radiotherapy. Three have died and none received chemotherapy. Two patients deteriorated rapidly and died with no further therapy.
CNS metastasis represents 1% and 4% of recurrences in patients treated according to protocols UKW-1, UKW-2. Data from UKW-3 is still accruing. CNS metastasis of Wilms' tumour is not in itself a terminal event, and as for other sites of recurrence, salvage therapy can be expected to be effective in patients without other adverse features. All surviving patients received radiotherapy and chemotherapy comprising etoposide and either ifosfamide or carboplatin.

P-106

SECRETING GERM CELL TUMORS OF THE CENTRAL NERVOUS SYSTEM (CNS GCTS): UPDATE OF THE COOPERATIVE GERMAN AND ITALIAN STUDY

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In 1993 international cooperation was initiated to establish a common protocol for diagnostic and treatment of malignant CNS GCTs. In the background of this initiative, 19 German and Italian children with secreting CNS GCTs were treated between January 93 and September 96.
Diagnostic, staging and treatment approach: ß-human chorionic gonadotropin (ß-HCG)>50 IU/l and/or alpha-fetoprotein (AFP)>25 ng/ml in the serum and/or in the CNS fluid (CSF) were considered as sufficient criteria for diagnosis. Staging procedures included CSF-cytology and MRI (head/spinal). Treatment consisted of 4xPEI: cisplatin 20 mg/m² day 1-5, VP16 100 mg/m² day 1-3 and ifosfamide 1.5 g/m² day 1-5. Surgery was recommended in case of residue after chemo- and before radiotherapy, which consisted of craniospinal irradiation (30 Gy) and tumor boost (20 Gy).
Patients: 14 boys and 5 girls were registered. Diagnosis by markers only was done in 6 patients (pts). 4/7 pts with significant marker elevation had biopsy showing germinoma. 6 children had primary resection and marker elevation. CSF-cytology was positive in 4 pts. Spinal metastases were detected in 2 pts. 14 pts had normalization of markers after 2 courses of PEI. A decrease of tumor volume was observed in 9 pts. In 8 children tumor diminished totally after 4 courses. Despite decrease of markers tumor growth was observed in 3 pts. Histology of the resected tumor was mature teratoma. Major side effect of treatment was transient leucopenia in 6 pts and severe infections in 2 children.
Results: All pts have finished treatment (median follow-up 12 months) with an EFS of 81±8%.
Conclusion: The achieved survival rates indicate the effectiveness of the used regimen. Since October 97 the official SIOP CNS GCT 96 protocol is started for treatment of secreting and germinomatous CNS GCTs. Up to February 24, 1997, 13 pts are registered in this study. After a longer follow-up first results of the SIOP CNS GCT study will be presented.
Supported by Deutsche Krebshilfe

P-107

PRIMARY CHEMOTHERAPY IN THE LONG TERM MANAGEMENT OF INTRAOCULAR RETINOBLASTOMA

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The association of Carboplatin (CBDCA) and Etoposide (E) has been found to be effective in the treatment of intraocular retinoblastoma (RB), permitting local therapy, or reducing retinic scarring after argon laser therapy, or avoiding radiotherapy, and enucleation. We report the results and the longer follow-up of 25 intraocular retinoblastomas, treated with CBDCA-VP16 association.
Since january 1990 to december 1996, 25 pts affected with intraocular RB have been treated with CBDCA-E association. CHT consisted of CBDCA (1,000 mg/sqm) and E (300 mg/sqm) on day 1, 21-28 days apart and reduced by 1/3 in pts weighing less than 10-12 kgs. Patients younger than 6 months received carboplatin at 25 mg/kg and etoposide 7 mg/kg. Twenty pts were at onset and five pretreated.
Eight pts (unilateral RB) received 4 courses of adjuvant CHT after enucleation because of risk factors. None relapsed after a mean of 27 months from diagnosis.
Seventeen pts (7 males, 10 females; mean age at diagnosis 5.7 mos, range 0-27 mos) received chemotherapy immediately followed by argon laser therapy, 15 of them had bilateral RBT, 4 had unilateral RBT. They received a mean of 6.6 courses of chemotherapy. After 2-4 courses of chemotherapy followed by argon laser 65.4% of major response patterns have been observed. Four patients are still under treatment.
Six pts had progressive disease under treatment: 3 received local RT and are alive without disease, 2 died of progressive disease after RT, 1 was lost to follow-up. All had bilateral RBT, 2 cases had familial disease, one had 13 cromosomial deletion, and one was pretreated with RT and platinum derivates.
Six no relapsed patients received neither RT nor enuclation after an average follow-up of 23 mos.
Five pts relapsed (4 bilateral 1 unilateral), 3 received further CHT courses with CBDCA-E and had complete remission pattern after a mean of 2 courses followed by argon-laser therapy; one pt received enucleation,and one RT, all are alive without disease.
In five patients (30%: 3 bilateral, 2 unilateral) no enucleation have been performed and at today they all are alive without disease.
Mielotoxicity was manageable and remains acceptable also for further courses in relapsed pts.
Conclusion:
- CBDCA-E appears effective also in relapsed patients
- The toxicity remains acceptable
- Enucleation could be delayed and in a few cases avoided
- Familial RBT seems to be less responsive to chemotherapy
- Longer follow-up is needed for the risk of second cancer

P-108

CONCOMITANT CHEMO-RADIOTHERAPY FOR CHILDHOOD ANAPLASTIC ASTROCITOMA (AA) AND GLIOBLASTOMA MULTIFORME (GM).

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Objective. Malignant gliomas are relatively uncommon (25% of CNS tumor) in pediatric age, but they share the same dismal prognosis of the adult population. Site of origin and invasiveness render a complete surgical resection rarely feasible; moreover post-surgical RT adds little benefit to outcome. Adjuvant CT demonstrated to be feasible and effective. To explore a possible synergic activity of RT and CT, a treatment program thus conceived was began. Methods. RT was administered on tumor site with conventional fractionation (180-200 cGy/d) at a median dose of 54Gy. Concomitant sequential CT included VP16 (250mg/sqm 30'-infusion x 2 doses) on day 1, ARAC (1.5g/sqm 30'-infusion) on day 8, IFO (5g/sqm 24h-continuous infusion) on day 15, CDDP (100mg/sqm 2h-infusion) on day 25, DACT (1mg/sqm iv) on day 40, for a total duration of 6-7 weeks. Results. Forty-one children (25 M, 16 F, median age 8yrs, range 2-15) were treated from 1987 to 1996. Diagnosis was AA in 30 cases and GM in 8; 3 brain stem (BS) tumors were radiologically diagnosed only. Site of disease was subtentorial in 25 cases (23 BS, 2 cerebellum), suvratentorial in 13 (10 hemispheric, 3 diencefalon), spinal in 3. In 38/41 pts a primary surgical approach was performed: 8 radical resection, 17 partial resection and 13 biopsy. In all the 23 pts with BS tumor a complete excision was unfeasible; with the exception of 1 case with a follow-up of 6mos, all of them died of their disease after a median time of 12 mos (range 3-27) from diagnosis. Four of 8 pts submitted to radical surgery were alive with a median follow-up of 23mos, while the others locally relapsed in 9-17mos. In the other 10 children with evaluable disease treatment applied obtained a 70% of response (3CR+4PR) and 4 pts were alive after a median time of 58mos from diagnosis. The overall survival at 2yrs with and without considering the pts with BS tumors were 30% and 58% respectively. Conclusions. Concomitant chemoradiotherapy did not obtain a better outcome than adjuvant RT only. Ameliorating AA/GM prognosis needs new treatment strategies.